Sorafenib-Induced Acute Pancreatitis in a Patient with Differentiated Thyroid Cancer

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What Is Known About This Topic?

- Several side effects have been described with the use of tyrosine kinase inhibitors like sorafenib. Nonetheless, only 9 cases of pancreatitis related to sorafenib treatment have been described, all of them with hepatocarcinoma and renal carcinoma treatment.

What Does This Case Report Add?

- This is the first case of sorafenib-induced pancreatitis described in the treatment of radioiodine-refractory thyroid cancer. We describe the 1-year follow-up after the resumption of treatment.

Keywords

Sorafenib · Tyrosine kinase inhibitor · Acute pancreatitis · Differentiated thyroid carcinoma · Iodine-refractory thyroid cancer

Abstract

Background: Sorafenib is a tyrosine kinase inhibitor approved for the treatment of metastatic renal cell carcinoma, hepatocellular carcinoma, and recently for radioactive iodine (RAI)-refractory metastatic differentiated thyroid carcinoma (DTC). Several side effects have been described including alterations in amylase and lipase levels. Nonetheless, only a few cases of pancreatitis during renal carcinoma and

hepatocellular carcinoma treatment have been described.

Objective: To describe the first case report of sorafenib-induced acute pancreatitis during the treatment of thyroid carcinoma. **Methods and Results:** In a 60-year-old Latin woman with RAI-refractory papillary thyroid carcinoma, T4b-N1bM1, sorafenib was indicated due to locally recurrent, metastatic, and progressive lung involvement without iodine uptake. Therapy was initiated (200 mg) every 8 h. Three days after starting the medication, abdominal pain, nausea, and emesis appeared. A blood test revealed elevated amylase (343 U/L RV: 28–100) and lipase (1,969 U/L RV: 23–300) levels, but no other findings, confirming acute mild pancreatitis. Hypertriglyceridemia, hypercalcemia, and alcohol and biliary etiologies were ruled out and sorafenib-acute pancre-

atitis was concluded. Two weeks later, sorafenib was resumed without recurrence. To date, this is the tenth sorafenib-related pancreatitis report and the first in a patient with RAI-refractory metastatic DTC. **Conclusions:** Sorafenib-acute pancreatitis may develop in patients with RAI-refractory thyroid cancer. This adverse event seems to be independent of the treatment duration and administered dose. Resuming the medication with an adjusted dose after pancreatitis resolution may be safe.

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Introduction

Sorafenib is a small molecular tyrosine kinase inhibitor, approved for the treatment of metastatic renal cell carcinoma and hepatocellular carcinoma since its approval by the US Food and Drug Administration in 2005. Recently, it demonstrated improvement in progression-free survival (PFS) in radioactive iodine (RAI)-refractory locally advanced or metastatic differentiated thyroid cancer (DTC), a setting for which it has been approved since November 2013. We present the case of a 60-year-old woman with a history of DTC with pulmonary and local progression, who presented with acute pancreatitis after recent use of sorafenib that resolved when the treatment was discontinued. To date, this is the first case report of sorafenib-induced acute pancreatitis during the treatment of DTC in progression.

Patient

A 60-year-old Latin woman with papillary thyroid carcinoma, T4bN1bM1 (ATA classification) attended our practice. She was initially treated by total thyroidectomy, central and left neck lymph node dissection, tracheal reconstruction, and subsequently RAI therapy (200 mCi) with local neck uptake and elevated stimulated thyroglobulin levels. There was no peripheral uptake, despite lung involvement seen on thorax tomography. After 3 years, a neck soft-tissue resection was performed with confirmed local recurrence. Concomitantly, during follow-up, lung metastases progression was documented. Sorafenib was indicated for the locally recurrent disease and metastatic and progressive lung involvement without iodine uptake. Therapy was initiated with 200 mg of oral sorafenib every 8 h.

Three days after starting the medication, the patient consulted the emergency department with abdominal pain, nausea, and emesis. A blood test revealed elevated amylase levels (343 U/L RV: 28–100) and lipase levels (1,969 U/L RV: 23–300) with no other findings, confirming acute mild pancreatitis. She had a normal abdominal ultrasound and a negative magnetic resonance cholangiopancreatography, ruling out biliary etiology. Hypertriglyceride-

mia, hypercalcemia, and alcohol etiologies were ruled out. She reported starting sorafenib 3 days before, taking 9 doses in total. She was also taking levothyroxine equivalent to 165 µg daily, calcium carbonate 600 mg daily, losartan 50 mg twice daily, omeprazole 20 mg daily, and acetaminophen with hydrocodone if needed, all of which had been used previously. Sorafenib was stopped and clinical evolution was favorable, with oral tolerance after 48 h of observation and no associated complications. She was discharged.

Two weeks later, the patient was assessed, with no clinical findings, and had normal amylase and lipase levels and liver function. We decided to restart sorafenib at a lower dose, continuing with clinical evaluation every 2 weeks, and deciding on augmentation according to tolerance. She completed 6 months of treatment with sorafenib at a dose of 200 mg every 12 h without complications, so the dose was increased to 200 mg every 8 h, with good tolerance. Currently, after 1 year of treatment, she has not developed any other complications. Recent blood tests are normal for pancreatic and hepatic function.

Discussion

Sorafenib is a tyrosine kinase inhibitor that intervenes in pathways of cell proliferation, apoptosis, and the vascular endothelial growth factor receptor (VEGFR)-2/platelet-derived growth factor receptor (PDGFR)-β signaling cascade which is involved in vasculogenesis, tumor cell motility, and metastasis [1]. Several side effects have been described including dermatological, cardiovascular, respiratory, gastrointestinal, hematological, and renal compromise, with different grades of severity [2]. However, the most common side effects consist of reversible skin rashes (in 40% of patients), diarrhea (43%), hand-foot syndrome (30%), and hypertension (17%). Asymptomatic and transient elevations in serum amylase and lipase are also very common, and have been described in different phase I and phase II clinical trials, varying between 20 and 45% and 27 and 55.7%, respectively. These elevations seem to depend on the drug dose and exposure [3–6]. Nonetheless, acute pancreatitis has been reported as an unusual complication, which appears to be independent of the dose and time of exposure. These first descriptions were identified in phase I clinical trials in which pancreatitis, as described above, appeared to be dose-related, with resolution after interruption of the drug [4, 5]. However, in one phase II clinical trial, in spite of an increase in amylase and lipase levels, no cases of pancreatitis were described [6]. A recent meta-analysis concluded that small-molecule VEGFR tyrosine kinase inhibitors were associated with the development of acute pancreatitis of varying severity when used during the treatment of a broad range of malignancies. This meta-analysis also

Table 1. Reported cases of acute pancreatitis during treatment with sorafenib

First author [ref.]	Year	Malignancy	Age, years/ gender	Dose	Length of exposure	Amylase/ lipase, U/L	Treatment	Pancreatitis recurrence
Amar [12]	2007	metastatic RCC	53/F	400 mg 2× daily	3 weeks	1,361/99	not known	not known
Li [9]	2007	metastatic RCC	80/M	400 mg 2× daily	4 weeks	156/>200	sorafenib resumed, 400 mg daily	acute pancreatitis
Saadati [13]	2010	HCC	53/M	unknown	4 weeks	118/484	no resumption	no recurrence
Kobayashi [14]	2011	metastatic RCC	71/M	400 mg 2× daily	2 weeks	973/2,733	no resumption	no recurrence
Sevin [15]	2013	metastatic RCC	69/F	400 mg 2× daily	10 days	244/1,014	change to sunitinib, 37.5 mg 2× daily	pancreatitis
Olayode [17]	2013	metastatic RCC	68/M	200 mg 2× daily	11 days	48/805	resumption	asymptomatic at 10 weeks
Wang [16]	2014	HCC	76/F	400 mg 1× daily	6 weeks	124/>3,000	sorafenib resumed, 200 mg daily	no recurrence
Chou [8]	2016	HCC	56/M	200 mg 1× daily	6 days	1,388/3,685	no resumption	no recurrence
Twohig [18]	2017	HCC	53/M	200 mg 2× daily	3 weeks, suspended for 3 days	148/4,379	no resumption	no recurrence
This study	2016	DTC	59/F	200 mg every 8 h	3 days	343/1,969	sorafenib resumed, 200 mg 2× daily, increased to 200 mg 3× daily	no recurrence

HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; DTC, differentiated thyroid carcinoma; F, female; M, male.

demonstrated that there was no significant effect on the type of neoplasm or the development of all-grade and high-grade pancreatitis [7].

There is no clear explanation to date for sorafenib-related pancreatitis. Authors have proposed a mechanism mediated by pancreatic ischemia involving VEGF, as it plays a role in pancreatic capillary vascularization and in regulating the cell cycle of the acinar cells. In this scenario, anti-VEGF activity could produce acinar cell apoptosis, causing the release of autodigestive enzymes and the resulting pancreatitis [8]. Alternatively, it has also been proposed that anti-VEGF activity generates duodenal-pancreatic reflux and, subsequently, the autodigestion of pancreatic tissue [9]. Boudou-Rouquette et al. [10], on the other hand, reported that higher cumulative doses of sorafenib are associated with a higher risk of developing sorafenib grade ≥ 3 toxicity in the presence of a genetic predisposition. Nevertheless, an individual idiosyncratic effect of the molecule cannot be ruled out [11].

We found 9 reports of sorafenib-related pancreatitis in the literature, 5 of them in patients with metastatic renal cell carcinoma and 4 in patients with hepatocellular carcinoma. The patients consisted of 6 males and 3 females aged between 53 and 80 years. Administered doses related to pancreatitis development were 400 mg twice daily in 4 patients, 400 mg daily in 1 patient, 200 mg twice daily in 2 patients, 200 mg daily in 1 patient, and an unknown dose in 1 patient; the mean time for pancreatitis onset was 20.1 days. In all cases, sorafenib was discontinued, and treatment resumed after pancreatitis resolution differed between cases. There was only 1 case in which sorafenib was discontinued for a leg skin rash, with the onset of pancreatitis occurring 3 days later [18]. In 4 patients, sorafenib was not resumed, and in 2 patients, it was restarted at half the previous dose; pancreatitis recurrence was documented in 1 of these patients. Another patient resumed sorafenib and no recurrence occurred until after 10 weeks of treatment [17]. Finally, in 1 patient, the treat-

ment was replaced with sunitinib, with pancreatitis recurrence. The case reports are shown in Table 1.

This is the first report of sorafenib-related pancreatitis in a patient with advanced thyroid carcinoma. Compared with other cases, there was a shorter time of exposure to the molecule, but the dose administered was in the range reported in previous cases. In our patient, we decided to resume sorafenib with a significant reduction, continuing with strict vigilance. To date, we can say that there has been no pancreatitis recurrence.

Conclusions

Based on previous experience, this is the tenth sorafenib-related pancreatitis report and the first in a patient with RAI-refractory metastatic DTC. In spite of a positive correlation between cumulative dose and the risk of other types of toxicity, it appears that pancreatitis can

occur relatively independently of the treatment duration and administered dose. In the follow-up of RAI-refractory metastatic DTC patients, the endocrinologist should be alert to the appearance of symptoms related to pancreatitis and the therapy should then be immediately discontinued. Resuming therapy appears to be safe, although more experience is needed to provide conclusive information.

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Disclosure Statement

All authors declare that they have no personal, political, ideological, academic, intellectual, commercial, or any other competing interests.

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