Journal of Oncological Science 2 (2016) 63–65

Contents lists available at ScienceDirect

Journal of Oncological Science

journal homepage: https://www.elsevier.com/locate/jons

Case report of a renal cell carcinoma patient with acute pancreatitis under both sunitinib and axitinib treatment

Utku Oflazoglu [a], Umut Varol [a], Ahmet Alacacioglu [a,*], Tarik Salman [a], Necla Demir [b], Huseyin Salih Semiz [b], Aziz Karaoglu [b], Ilhan Oztop [b]

[a] Department of Medical Oncology, Izmir Katip Celebi University Ataturk Training and Resarch Hospital, Izmir, Turkey
[b] Department of Medical Oncology, Dokuz Eylul University, Izmir, Turkey

ARTICLE INFO

Article history:
Received 25 April 2016
Accepted 28 July 2016
Available online 24 September 2016

Keywords:
Sunitinib
Axitinib
Renal cell carcinoma
Pancreatitis
Side effects

ABSTRACT

Sunitinib and axitinib are oral tyrosine kinase inhibitors (TKI) that is commonly used in the treatment of metastatic renal cell carcinoma (RCC) as it has been shown to improve the progression-free survival of patients compared with sorafenib. Hypertension, palmar-plantar erythrodysesthesia, diarrhea, decreased appetite, nausea, and fatigue are common adverse events associated with them. We declared the first case report of a RCC patient with acute pancreatitis both under sunitinib and axitinib treatment. A 63-year-old male RCC patient who had been previously treated with interferon alfa 2b, sunitinib, everolimus and axitinib was hospitalized for acute pancreatitis four months after the onset of sunitinib therapy and five months after the onset of axitinib treatment. Symptoms and levels of serum lipase were normalized within one week after drug was withheld. Acute pancreatitis is a rare side effect of TKI and because of this, in patients under TKI treatment abdominal pain should be considered as a possible symptom of acute pancreatitis.

1. Introduction

Sunitinib is an oral tyrosine kinase inhibitor that is commonly used in the treatment of metastatic renal cell carcinoma (RCC). Axitinib is an oral second-generation selective inhibitor of vascular endothelial growth factor receptors (VEGF) 1, 2, and 3, platelet-derived growth factor receptor-α, and c-kit which have recently been approved for the treatment of advanced renal cell carcinoma. It was endorsed for the treatment of advanced renal cell carcinoma as it has been shown to improve the progression-free survival of patients compared with sorafenib.[1,2] Hypertension and palmar-plantar erythrodysesthesia are known adverse events associated with sunitinib. Diarrhea, hypertension, hand–foot syndrome, decreased appetite, nausea, and fatigue are common adverse events associated with axitinib.[3]

Acute pancreatitis is an acute inflammatory process of the pancreas. It can range from mild interstitial pancreatitis to severe pancreatitis with concomitant multi-organ failure including pancreatic necrosis. It is typically rapid in onset but exhibits a mild and self-limiting character. The patients may present with elevated serum amylase and lipase levels, mild to severe epigastric pain often radiating to the back, and inflammatory changes visualized on computed tomography or magnetic resonance imaging. The most common causes of pancreatitis are biliary stones and alcohol consumption, with each accounting for about 30–40% of the cases. Additionally, trauma to the pancreas resulting from abdominal injury or post-endoscopic retrograde cholangiopancreatography may also cause acute pancreatitis. Hypertriglyceridemia, hypercalcemia and infection are much less common causes of pancreatitis, each contributing to less than 1% of the cases.[4,5] Another uncommon cause of this inflammation is drug-induced pancreatitis with reported incidences ranging from 0.1% to 2%. Sulfonamides, furosemide, tetracyclines and corticosteroids are some examples associated with pancreatitis. In cancer patients, pancreatitis may occur due to medications or metastases to the pancreas. There are various reports of pancreatitis secondary to chemotherapy treatment, including paclitaxel, ifosfamide, vinorelbine, cisplatin, cytarabine and L-asparaginase.[6] Several cases of nonselective tyrosine kinase inhibitor induced acute pancreatitis (sorafenib, sunitinib etc) have been reported.[7–9] However, there was only one case that has been reported with an axitinib treatment. We declared the first case report of a RCC

* Corresponding author.
E-mail address: dralaca2000@yahoo.com (A. Alacacioglu).
Peer review under responsibility of Turkish Society of Medical Oncology.

http://dx.doi.org/10.1016/j.jons.2016.07.002

patient with acute pancreatitis under both sunitinib and axitinib treatment.

2. Case report

A 63-year-old male patient with renal cell carcinoma had hypertension, hypothyroidism and a history of thyroid papillary cancer. The patient was a nonsmoker and did not drink alcohol before. He was receiving calcium channel blocker and alpha blocker for hypertension and L-thyroxine for hypothyroidism. Metastatic relapse occurred in two years following a nephrectomy for locally advanced renal cancer. The patient exhibited liver and lung metastases. He was first treated with interferon alfa 2b for three months. Given the cancer progression, we stopped the interferon treatment and preferred sunitinib as a second line treatment.

At the onset of sunitinib treatment, the patient displayed a good functional status with Eastern Cooperative Oncology Group (ECOG) performance score 1 and recovered from the toxicity associated with the previous therapies. The patient was dosed 50 mg po sunitinib daily through 4 weeks of treatment and 2 weeks of rest. One month after the onset of sunitinib treatment, we reduced the dose of sunitinib due to grade 3 fatigue and hand-foot syndrome. Thereafter, treatment resumed with continuous 37.5 mg po daily without scheduled breaks. The best objective response with sunitinib was stabilized disease.

Four months after the onset of sunitinib therapy, the patient was hospitalized in the emergency department for abdominal pain and nausea. The pain emerged in the epigastric area and moved to the back and all abdomen within 1 h after the meal. The patient had no fever and no sign of bowel obstruction. White blood cell count was elevated at 14.5×10^9/l, hematocrit (39%; reference range: 41–53%) and platelet counts were within normal limits (326 000 mm^3; reference range: 156–373 000 mm^3). Creatinine was at its baseline level of 1.06 mg/dl. Liver function tests were normal. The amount of lipase was elevated at 244 U/l (reference range: 0–38 U/l). Blood glucose level remained within the normal range. The level of C-reactive protein was elevated at 90 mg/l. Calcium (8.8 mg/dl) and triglyceride (140 mg/dl) levels fell within normal ranges.

An abdominal ultrasonography (USG) showed that the gallbladder was acalculous and free from sludge. A computed tomography (CT) scan of the abdomen revealed a low-density edema and an enlarged pancreatic tail, with a heterogeneity of surrounding fat (Fig 1). The CT scan revealed no evidence of gallstones, cholecystitis or choledocholithiasis.

The patient was requested to fast, with fluid hydration and administration of electrolytes, and pain medication as needed for symptom relief, and sunitinib was withheld. Symptoms were revealed and blood lipase levels were normalized within a few days. After discharge from the hospital, sunitinib was not used anymore and axitinib was introduced as a third-line treatment.

At the onset of axitinib treatment, the patient had a good functional status (ECOG score 1) and recovered from the toxicity of the previous therapies. We increased the dose of axitinib from 5 mg twice daily to 10 mg twice daily after 14 days. At the first interval radiologic evaluation, we found that the disease was stabilized. However, five months after the onset of axitinib therapy, the patient was again hospitalized in the internal medicine department for abdominal pain. The pain was characterized by a similar localization and spread. White blood cell count was elevated at 8.6×10^3/l, hematocrit (39%; reference range: 41–53%) and platelet counts were normal (396 000 mm^3; reference range: 150–400 000 mm^3). Liver and renal function tests were normal. The amount of lipase was again elevated at 257 U/l (reference range: 73–393 U/l). The level of C-reactive protein was elevated at 115 mg/l. Blood glucose, calcium, triglyceride levels fell within normal ranges. An abdominal USG and CT scan revealed images compatible with acute pancreatitis without any signs of gallstones, cholecystitis or choledocholithiasis (Fig 2). Axitinib was withheld and the patient was treated with the same previous approach that included fluid and electrolytes administration.

3. Discussion

Sorafenib and sunitinib are multikinase inhibitors and have been shown in association with acute pancreatitis in many clinical reports. The mechanism of acute pancreatitis is unclear. It may include pancreatic ischemia associated with the antiangiogenic effect and a reduction in the protective effect of VEGF as well as the platelet-derived growth factor, which would increase the severity of pancreatitis.[10,11] Another hypothesis suggests that thyrosine kinase inhibitors may cause gastrointestinal motility abnormalities which, in turn, may trigger a reflux of the duodenal contents into the pancreatic duct.[12] Axitinib is a small molecule tyrosine kinase inhibitor of VEGF receptors and has been shown to significantly inhibit VEGF-mediated endothelial cell proliferation and cancer cell survival. Axitinib might induce acute pancreatitis through the same mechanism as sorafenib and sunitinib. It is yet to be answered whether acute pancreatitis due to tyrosine kinase inhibitors is associated only with sorafenib and sunitinib or whether it may also be caused by other drugs of the same class. It is also unclear whether the mechanism is common to all anti-VEGF tyrosine kinase inhibitors.

This is the second report of axitinib-induced pancreatitis. In the absence of any other recognized etiology, one might infer that the case of pancreatitis reported was likely caused by axitinib. The rapid clinical and biological recovery of the patient after axitinib discontinuation was another argument to attribute pancreatitis to axitinib intake.[13] In our opinion, physicians should anticipate acute pancreatitis when patients complain of acute abdominal pain on treatment with axitinib; and acute pancreatitis should be added to

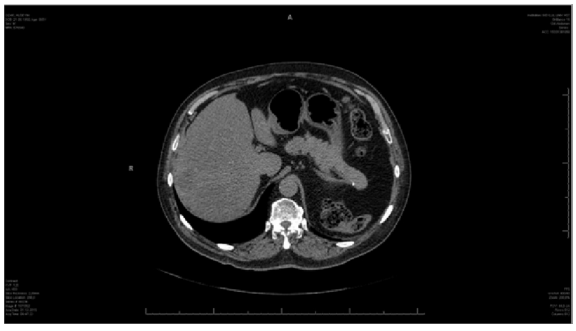

Fig. 1. Image of acute pancreatitis of the patient under sunitinib treatment

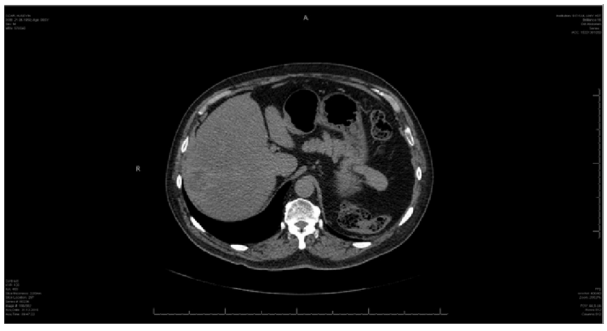

Fig. 2. Image of acute pancreatitis of the patient under axitinib treatment

the list of potential axitinib-related adversities with an unknown frequency.

References

1. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: Overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol*. 2013;14:552–562.
2. Facchini G, Perri F, Caraglia M, et al. New treatment approaches in renal cell carcinoma. *Anticancer Drugs*. 2009;20:893–900.
3. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomised phase 3 trial. *Lancet*. 2011 Dec 3;378(9807):1931–1939.
4. Whitcomb DC. Acute pancreatitis. *N Engl J Med*. 2006;354:2142–2150.
5. VanWoerkom R, Adler DG. Acute pancreatitis: Review and clinical update. *Hosp Physician*. 2009;45:9–19.
6. Morgan C, Tillett T, Braybrooke J, et al. Management of uncommon chemotherapy-induced emergencies. *Lancet Oncol*. 2011;12:806–814.
7. Pezzilli R, Corinaldesi R, Morselli-Labate AM. Tyrosine kinase inhibitors and acute pancreatitis. *JOP*. 2010;11:291–293.
8. Saadati H, Saif MW. Sorafenib-induced acute pancreatitis. *JOP*. 2010;11:283–284.
9. Ueda T, Takeyama Y, Yasuda T, et al. Vascular endothelial growth factor increases in serum and protects against the organ injuries in severe acute pancreatitis. *J Surg Res*. 2006;134:223–230.
10. Pierce GF, Mustoe TA, Lingelbach J, et al. Platelet-derived growth factor and transforming growth factor-beta enhance tissue repair activities by unique mechanisms. *J Cell Biol*. 1989;109:429–440.
11. Li M, Srinivas S. Acute pancreatitis associated with sorafenib. *South Med J*. 2007;100:909–911.
12. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: An evidence-based review. *Clin Gastroenterol Hepatol*. 2007;5:648–661.
13. Britten CD, Kabbinavar F, Hecht JR, et al. A phase I and pharmacokinetic study of sunitinib administered daily for 2 weeks, followed by a 1-week off period. *Cancer Chemother Pharmacol*. 2008;61:515–524.