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Case Report Open Access

mTOR Inhibitor Everolimus Causing Diabetic ketoacidosis and Acute Pancreatitis

Hui Ma[1], Zhenggang Ren[1], Jiyao Wang[2], Xizhong Shen[2] and Lei Li[2*]

[1]*Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, 200032, China*

[2]*Department of digestion, Zhongshan Hospital, Fudan University, Shanghai, 200032, China*

Abstract

Everolimus, an mTOR inhibitor, has received approval for used in hormone receptor positive advanced breast cancer treated with nonsteroidal aromatase inhibitors by FDA. This report presents a case of a 49-year-old woman being treated with everolimus and aromasin for advanced breast cancer who developed diabetic ketoacidosis and acute pancreatitis. The incidence and management of diabetic ketoacidosis and acute pancreatitis are discussed. Careful monitoring of blood glucose and lipid levels and dose adjustments of everolimus together with glucose-lowering and lipid-lowering therapy can allow patients to continue this medication. Increasing indications for use of mTOR inhibitors, the common and serious side effects must be cognized by prescribing clinicians.

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Introduction

Everolimus is an inhibitor of mTOR, a serine-threonine kinase downstream of the PI3K/AKT pathway that is critical for cell growth and angiogenesis.[1-2]And it was approved by the FDA for use in several cancers, including renal cell carcinoma, neuroendocrine tumor and breast cancer and so on.[3-5] With expanding indications for everolimus use, the common and serious side effects should be cognized by prescribing clinicians.

Case Report

A 49-year-old woman with a metastatic breast cancer being treated with everolimusat 10mg daily and aromasin 25mg daily for the past 2 months, present to the emergency department with shortness of breath and vomiting of 6 hours, without fever, chest tightness, chest pain, abdominal pain, hematemesis, jaundice, dizziness or headache.

She was initially diagnosed with breast cancer 3 years ago, when she present with a mass of the left breast. Modified radical mastectomy was performed and postoperative pathological diagnosis revealed it a breast infiltrating ductal carcinoma (3cm*1.5cm*1cm), with ER (+ 60%), PR (+50%) and HER-2 (+/-). Multiple metastases to lymph nodes, lungs, liver and bone were found by PET/CT at follow-up 2 months ago. The doctor therefore initiated therapy with everolimus and aromasin. After starting everolimus, she had no common side effects of anorexia, diarrhea, fatigue, skin rash and oral ulcer approximately 2 months. Lymph nodes, lungs, liver and bone metastases were all smaller compared with prior imaging, with obviously decreasing fluorodeoxyglucose metabolism, detected by PET/CT 4 days before hospitalization.

The patient was otherwise healthy with no medical problems, including no personal or family history of diabetes and pancreatitis. She did not consume alcohol or smoke tobacco. Fasting laboratory results 1 year ago before hospitalization showed her blood glucose level (6.3mmol/L)slightly higher than normal (3.9-5.6mmol/L), total cholesterol level of 8.47mmol/L (normal <5.2mmol/L) and triglyceride level of 4.64mmol/L (normal 0.6-1.7mmol/L). Her medications on hospitalization were everolimus 10mg daily and aromasin 25mg daily, without any glucose-lowering and lipid-lowering therapy.

Laboratory results showed a blood amylase level of 665U/L (normal <220U/L), PH level of 6.96 (normal 7.35-7.45), glucose level of 29.1mmol/L (normal 3.9-5.6mmol/L) and ketone body level of 1.96mmol/L (normal 0.03-0.3mmol/L), with white blood cell count and C-reactive protein obviously greater than normal. A CT scan of abdomen showed exudation around the pancreas and renal fascial thickening. She was diagnosed with diabetic ketoacidosis and acute pancreatitis.

The patient was managed supportively with bowel rest, intravenous fluids, intravenous insulin, pancreas secretion inhibition, acidosis correction and nutrition support. Everolim us and aromasin were held. Shortness of breath and vomiting resolved after several hours, and lipase decreased to 67 U/L and blood ketone body to 1.49mmol/L after 3days.Her total cholesterol level of 6.26 mmol/L and triglyceride level of 3.61 mmol/L were still higher than normal after nearly 1 week of bowel rest, but the levels of onset were not evaluated. Then she was started a diabetes and liquid clear diet after 1 week. Her blood ketone body and urine ketone body were monitored closely and they return to normal level nearly 1 month after hospitalization, with insulin therapy. At the time of discharge, abdomen CT reexamination disclosed the pancreas exudation disappeared completely.

The patient was then restarted on everolimus at a lower dose of 5 mg daily, and aromasin at the same dose of 25mg daily. She was concurrently started on atorvastat in 20mg daily and insulin determine 14U daily. With closely monitoring her blood glucose and liquid levels, her condition was stable after 3 months.

Case Report

Everolimus is an inhibitor of mTOR, a serine-threonine kinase downstream of the PI3K/AKT pathway that is critical for cell growth

***Corresponding Author:** Dr. Lei Li, Department of digestion, Zhongshan Hospital, Fudan University, Shanghai, 200032, China; E-mail: li.lei@zs-hospital.sh.cn

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and angiogenesis. Everolimus binds an intracellular protein, leading to inhibition of mTORkinase activity. Additionally, everolimus inhibits expression of hypoxia inducible factor and reduces vascular endothelial growth factor expression [1-2].

Everolimus was initially approved by the FDA in 2009 for the second line treatment of advanced renal cell carcinoma. Subsequently, it has received approval for use in subependymal giant cell astrocytomas associated with tuberous sclerosis, progressive pancreatic neuroendocrine tumor, and renal angiomyolipoma with tuberous sclerosis complex. In 2012, everolimus was approved by the FDA, treated with nonsteroidal aromatase inhibitors, for use inhormone receptor positive and human epidermal growth factor receptor-2 (HER2) negative advanced breast cancer. Common side effects of everolimus include stomatitis, rash, diarrhea, fatigue and upper respiratory tract infections [2-3].

Recent phase III studies across several tumor types have shown that hyperglycemia and hypertriglyceridemia are common side effects of everolimus therapy. In the landmark trail for renal cell cancer (RECORD-1), taking everolimus at 10mg daily, 50% (135/269) patients had hyperglycemia, while 71% (191/269) hypertriglyceridemia. [4]In the BOLERO-2 trial in patients with advanced breast cancer, 4% (13/482) of patients receiving everolimus and exemetane developed grade3 hyperglycemia, and 0.8% (4/482)developed grade3 hypertriglyceridemia [6].

The pathophysiology of mTOR inhibitor-induced hyperglycemia is complex. mTOR and its downstream target S6 kinase 1 interact with various growth factors, hormones and nutrients to regulate protein translation and cell growth, proliferation and apoptosis. [7]In animal models, mTOR inhibitor sirolimus induces diabetes mellitus by increasing insulin resistance, glucose intolerance, and gluconeogenesis, and reducing β-cell function.[7-8]Without glucose-lowering therapy if necessary, hyperglycemia may lead to life-threatening complications, such as diabetic ketoacidosis, hyperosmolar hyperglycemic state and lactic acidosis. In this case, the patient had hyperglycemia before starting everolimus, without any glucose monitoring or glucose-lowering therapy during the treatment of everolimus, finally worsening hyperglycemia leaded to diabetic ketoacidosis.

The pathogenesis of hypertriglyceridemia associated with mTOR inhibitor is poorly understood but may be related to degradation of apolipoprotein B100reduced. Apoipoprotein B100 is formed in the liver and is essential to the assembly of very low-density lipoproteins. [9]Additionally, everolimus may lower levels of lipoprotein lipase activity and increase free fatty acid levels, which can contribute to dyslipidemia. Hypertriglyceridemia is the third most common cause of acute pancreatitis, after alcohol and gallstones. The mechanism by which hypertriglyceridemia leads to acute pancreatitis is unclear, but is believed to be related to the impaired clearance of chylomicrons, leading to pancreatic capillary hyperviscosity, and then leading to ischemia. Alternative hypotheses suggest that pancreatic lipase hydrolyzes excess triglycerides, causing damaging free fatty acids to accumulate in the pancreas, or the triglycerides themselves contribute to inflammation within the pancreas.[2,10]In this case, the patient had hypertriglyceridemia before starting everolimus, without any lipid monitoring or lipid-lowering therapy during the treatment of everolimus, and hypertriglyceridemia was considered to be the main cause of acute pancreatitis, after eliminating other possible causes.

No formal guideline is available on the management of mTOR inhibitors induced diabetic ketoacidosis or pancreatitis. As with other causes of diabetic ketoacidosis and acute pancreatitis, management strategies include bowel rest, intravenous fluids, intravenous insulin, pancreas secretion inhibition, acidosis correction, prophylactic antibiotics and nutrition support. And the patients should stop taking everolimus, when improved they are advised to restart on everolimus with careful monitoring of blood glucose and lipid levels and dose adjustments.

Summary

To the authors' knowledge, this is the first reported case of everolimus-induced diabetic ketoacidosis and everolimus-induced acute pancreatitis occurring synchronously or successively in short time. Hyperglycemia and hypertriglyceridemia are common side effects of everolimus, and elevations in glucose and lipid levels can both lead to life-threatening complications. With expanding indications for everolimus use, prescribing oncologists must be cognizant of common and serious side effects. Glucose and lipid levels should be monitored regularly, and glucose-lowering and lipid-lowering therapy or dose adjustments of everolimus, or both, can allow patients to continue this medication in the setting of hyperglycemia and hypertriglyceridemia.

Competing Interests

The authors declare that they have no competing interests.

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