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Abstract

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<Case report>

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We adhere to the journal's code of ethics.

Abstract: A case with non-small cell lung cancer exhibited extreme hyperglycemia after lorlatinib treatment, whose adverse effects on hyperglycemia is little known. But, the lorlatinib could be continued by intensifying diabetes treatment, indicating the importance of glucose monitoring during lorlatinib administration, and of adequate intensification of treatment for such hyperglycemia.

Key Message:

The present case indicated that 1) glucose monitoring is warranted during lorlatinib treatment, and 2) importance of adequate intensification of treatment for hyperglycemia after the lorlatinib treatment.

Introduction

Many countries face a worldwide increase in individuals with diabetes mellitus, as well as those with lung cancer. Lung cancer is one of the leading causes of death worldwide (1), and 8–18% of cancer patients are reported to have diabetes mellitus (2). Therefore, adequate management of comorbid diabetes is important for the treatment of cancer. Approximately 5% of non-small cell lung cancers (NSCLC) are reported to exhibit aberrant arrangement of the gene for anaplastic lymphoma kinase (ALK) (3-5). As a treatment for NSCLC, lorlatinib, a third-generation ALK tyrosine kinase inhibitor (TKI) that inhibits ALK and c-ros oncogene 1 (*ROS1*), has been clinically available for patients with mutations/arrangements of the ALK gene, usually called ALK-positive NSCLC.

Since the advent of the clinical use of lorlatinib, relatively unique adverse events associated with this medication have been recognized for metabolic phenotypes, such as hypercholesterolemia (82.4%) and hypertriglyceridemia (60.7%) (6). In a Phase 2 study, however, hyperglycemia was observed as an adverse event in 6 (2.2%) out of 275 patients receiving lorlatinib (7), 4 in Grade 1-2 (1.5%), and 2 in Grade 3 (0.7%), but none in Grade 4, according to the Common Terminology Criteria for Adverse Events (CTCAE v.4.03). Herein, we report a case of concomitant diagnosis of NSCLC and diabetes mellitus, whose glycemic control had been well-controlled, but whose glycemic level markedly increased after the initiation of lorlatinib, resulting in hyperglycemia equivalent to G4. However, treatment with lorlatinib could be continued without dose reduction by appropriate treatment for hyperglycemia.

Case Report

A 70-year-old man whose type 2 diabetes mellitus was treated by vildagliptin 50 mg, dipeptidyl peptidase-4 inhibitor (DPP4I) with an HbA1c level of 5.4– 6.7%, was diagnosed with abnormal lung opacity on chest computed tomography (CT) in the process of examination for cough, in January X-2 year. He was subsequently diagnosed with cT4N3M1a cStage IVA lung adenocarcinoma (NSCLC). The patient was positive for ALK gene translocation, and alectinib was started as first-line therapy, with a response of CR (graded New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline (version 1.1)) without major adverse events. Chest CT in March X year showed an increase in the size of the lower left lobe tumor, which was therefore judged as progressive disease (PD). Lorlatinib 100 mg/day was started as a second-line therapy in March X year. His blood glucose control was stable, with a casual blood glucose level of 167 mg/dL and an HbA1c level of 6.4%. At a regular visit to our hospital on June X (day 92 after initiation of oral administration of lorlatinib), he had thirst without any other symptoms, but his glycemic control had markedly deteriorated: 545 mg/dL of casual blood glucose and HbA1c 16.1%, and he was admitted to the hospital for treatment of hyperglycemia. (Table 1) Present symptoms on admission included: Height 171.5 cm, weight 83.5 kg (82.2 kg before the start of Lorlatinib), body mass index 28.4, clear consciousness, blood pressure 165/88 mmHg, heart rate 104 times/minute, respiratory rate 16 breaths per minute, SpO2 97% (room air), body temperature 35.9 .

Blood test results at admission were as follows: leukocyte count, 7540/μL; Hb, 10.3 mg/dL; Cr, 1.26 mg/dL; CEA, 13.0 Â ng/mL; CYFRA, 4.3 ng/mL; anti-GAD antibody, below the measurement sensitivity; C peptide 7.3 ng/mL. Chest CT showed a reduction in the size of the tumor. (Fig. 1)

Post-hospital course: At admission, his blood glucose level was as high as 500 mg/dL. The patient did not exhibit obvious overeating or weight gain, and the anti-GAD antibody test results were negative. CT imaging demonstrated no signs of pancreatic tumor(Fig. 1), and the serum C-peptide level was maintained Therefore, we suspected that the type 2 diabetes mellitus was exacerbated by the oral administration of lorlatinib. (Table. 1). Naranjo score was 5 (Table 2.) (8), which also suggest lorlatinib had good probability of this adverse event.

To control his hyperglycemia, intensive insulin therapy (multiple daily injections of insulin) was started, while lorlatinib was continued. Based on the consideration of his reduced renal function, vildagliptin was changed to linagliptin. Finally, his blood glucose level was controlled by injecting a rapid-acting insulin analog each premeal (Insulin Lispro 30-20-20 units) and basal insulin (glargine 18 units) at bedtime, with

oral administration of linagliptin after breakfast. His fasting blood glucose level was approximately 160 mg/dL, and the level before the meal were 170–200 mg/dL. To treat hypertriglyceridemia and hyperlipidemia, pemafibrate and ezetimibe were started in addition to pitavastatin. He was discharged from the hospital on the 12th day. Subsequently, partial response (PR) to lorlatinib was maintained for 6 months, and his glucose levels and lipid profiles were well controlled, with HbA1c levels of 7.0 to 6.6%, TG levels of 342–251 mg/dL, and LDL levels of 304–151 mg/dL.

Discussion

The present case exhibited extreme hyperglycemia after initiation of lorlatinib, a new anti-cancer medication class for NSCLC. Lorlatinib has well-known adverse effects on lipid metabolism, but less frequent and less severe events on glucose metabolism, despite its effects on body weight. The effectiveness of lorlatinib on lung cancer in the present case was apparent, and the patient could continue lorlatinib treatment with adequate intensification of the diabetes treatment. The present case highlights two clinical issues related to lorlatinib treatment, especially in those with diabetes mellitus.

First, administration of lorlatinib could lead to the deterioration of hyperglycemia. Excessive hyperglycemia might be more clinically relevant than the deterioration of dyslipidemia. The former could lead to hyperglycemia-associated symptoms and dehydration over a shorter period than dyslipidemia, which may affect the quality of life (QOL), as in the present case. Interestingly, one case was reported to have aggravated glycemic control after administration of ceritinib, another ALK inhibitor, for lung cancer treatment (9). Taken together, physicians may need to pay attention to glucose metabolism, in addition to the lipid profile, in patients taking lorlatinib, and monitoring of glucose levels would be warranted for patients receiving this medication, especially for those with diabetes mellitus.

Another clinical issue is the importance of intensifying diabetes treatment at the elevation of glucose levels after lorlatinib treatment. In the present case, the effect of lorlatinib on NSCLC was clinically evident for three months, when he exhibited excessive hyperglycemia equivalent to Grade 4. Then, the intensive insulin treatment was started with a relatively high dose of insulin (88 units/day: 1.05 units/kg/day), in addition to DPP4I. By adequate intensification of the treatment for hyperglycemia, he continued lorlatinib for the following six months after discharge, and his lung cancer had maintained PR within six months. Thus, adequate management of diabetes would allow the continuation of lorlatinib, and we may well consider intensifying diabetes treatment in the face of elevated glucose levels during the administration of lorlatinib.

It is of clinical concern how the lorlatinib could be associated with the deterioration of glucose metabolism. In the phase 2 study, hyperglycemia was reported in only 6 of the 275 patients; four patients (1.5%) in G1-2, two patients (0.7%) in G3, and none (0%) in G4 (6). In contrast, an increase in body weight was more frequently detected in the phase1/2 study, that is, 87 individuals (30.9%) among the 282 patients had a 10%–20% increase in their baseline body weight and 38 (13.5%) had a >20% increase in their baseline body weight (7). In the present case, the observed body weight gain during the detection of his extreme hyperglycemia was merely 1 kg, compared to before starting lorlatinib. However, his body weight increase was probably more than that observed (1kg), as his excessive hyperglycemia could have led to bodyweight reduction. Given that he had no sign of edema, this incremental increase in body weight was likely due to increased adipose tissue, which could enhance insulin resistance, leading to hyperglycemia. The worsening of his insulin resistance was supported because he required a relatively high dose (88 units/day: 1.05 units/kg/day) insulin injection. Although our search did not find any case reports of exacerbation of hyperglycemia related to lorlatinib, a relatively common frequency of body weight increase (44.4%) should indicate that more cases experience deteriorated glucose control after lorlatinib administration. Although glycemic control of diabetic patients is affected by various factors, there were no known side effects on psychiatric symptoms of lorlatinib or no obvious changes in lifestyle in this case, the present deterioration of his glycemic control was considered as a side effect due to lorlatinib.

In summary, the present case exhibited extreme hyperglycemia after lorlatinib treatment for ALK-positive NSCLC. By intensifying his diabetes treatment, he was able to continue to take lorlatinib with PR after

discharge. The present case showed two relevant points: glucose monitoring is warranted after the start of treatment with lorlatinib, especially for those with diabetes mellitus, and adequate management of diabetes can allow the continuation of lorlatinib for cases in which lung cancer is effectively treated. The mechanism by which lorlatinib causes hyperglycemia remains unclear and should be examined in the future.

Footnotes

Contributions: The first two authors, YN and MMI, were involved in the case of the patient in the ward, with supervision of IG and TF. All authors contributed to the final manuscript regarding the interpretation of the outcomes and conclusions. YN searched PubMed for relevant studies and wrote the manuscript under the supervision of MMI, IG, and TF.

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Table 1 Changes in metabolic parameters

Table1: Changes in Blood glucose, HbA1c, TG, LDL and Body weight	Table1: Changes in Blood glucose, HbA1c, TG, LI
year/month	X-1/6 X/2
BG (mg/dL)	120-160
HbA1c (%)	5.8-6.7
TG (mg/dL)	

Table1: Changes in Blood glucose, HbA1c, TG, LDL and Body weight	Table1: Changes in Blood glucose, HbA1c, TG, LI
LDL (mg/dL) BW (kg)	67

BG, blood glucose; TG, triglyceride; LDL, low-density lipoprotein cholesterol; BW, body weight.

Fig. 1 Chest and abdominal Computer Tomography (CT)

A. Chest CT in March X years showed an increase in tumor size in the left lower lobe.

B. Chest CT on June X showed a reduction in tumor size.

C. No pancreatic tumor was found on abdominal CT in June X.