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CASE REPORT

Nilotinib exacerbates diabetes mellitus by decreasing secretion of endogenous insulin

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Abstract We report a 74-year-old female with chronic myelogenous leukemia (CML) in accelerated phase with pre-existing severe type 2 diabetes (T2D) and hemorrhagic gastric ulcers who was successfully treated with nilotinib. We first considered second-generation tyrosine kinase inhibitors for the treatment of this patient, as they elicit a superior response compared with imatinib. We next selected nilotinib, rather than dasatinib, since the increased risk of bleeding associated with dasatinib represented a greater risk of fatality than aggravation of T2D with nilotinib. After improvement of hemorrhagic gastric ulcers and T2D with exogenous insulin therapy, we began nilotinib administration; insulin dose was increased to maintain her glucose levels whereas urine C-peptide level decreased. Conversely, when nilotinib was discontinued due to liver dysfunction, the dosage of injected insulin was decreased and urine C-peptide levels increased. After restarting nilotinib, the required dose of insulin gradually increased again, and urine C-peptide level decreased, indicating that nilotinib may have impaired secretion of endogenous insulin. The patient obtained a complete cytogenetic response after 3 months of nilotinib treatment. Her T2D has since been well controlled by insulin therapy. To our knowledge, this is the first report that nilotinib treatment for patients with severe T2D may induce a reversible decrease in endogenous insulin secretion, although the precise underlying mechanisms remain unknown. We highly recommend sufficient screening and early intervention with exogenous insulin therapy for diabetic CML patients who receive nilotinib.

Keywords Nilotinib · Insulin secretion · Diabetes mellitus · Chronic myelogenous leukemia

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Introduction

The advent and approval of tyrosine kinase inhibitors (TKIs), such as imatinib that has selectivity for BCR-ABL, has dramatically improved the life expectancy of chronic myeloid leukemia (CML) patients [1, 2]. The second-generation TKI nilotinib is a rationally designed inhibitor of BCR-ABL with approximately 20- to 50-fold higher potency and selectivity for BCR-ABL than imatinib [3]. Several studies have demonstrated that nilotinib is an efficacious and well-tolerated drug that produces little, if any, major side effects in the vast majority of CML patients [4–7]. The most common non-hematologic side effects reported for nilotinib are skin rash, pruritus, headache, nausea, and fatigue [4–7]. Frequent laboratory abnormalities observed during treatment with nilotinib include hyperbilirubinemia as well as elevated pancreatic enzymes and fasting glucose (FG) levels in a considerable number of patients [8]. Recently, large trials have reported that hyperglycemia induced by nilotinib is usually mild, transient, and manageable and does not lead to discontinuation of treatment in patients with or without pre-existing type 2 diabetes (T2D) [2, 9]. However, CML patients with severe

diabetes might have been excluded from these clinical trials, and the actual changes in glucose metabolism parameters have not been determined in more advanced diabetic CML patients. In this report, we present a case of CML with pre-existing severe T2D and hemorrhagic gastric ulcers, and we have clearly shown that nilotinib exaggerated T2D by causing decreased secretion of endogenous insulin. However, we were able to manage this side effect with exogenous insulin.

Case presentation

In March 2012, a 74-year-old woman with hemorrhagic gastric ulcers, hyperglycemia, and leukocytosis was referred to our hospital. She had been diagnosed with T2D in 1997, and her diabetes had been well controlled by treatment with pioglitazone hydrochloride, voglibose, and glibenclamide. However, her FG levels gradually increased, and it finally went up to approximately 300 mg/dl in December 2011. For flare-ups of T2D, she received additional sitagliptin phosphate hydrate. In March 2012, she complained of epigastralgia and was diagnosed with hemorrhagic gastric ulcers after upper gastrointestinal endoscopy. At this time, since thrombocytosis and leukocytosis were noted in addition to anemia due to hemorrhagic gastric ulcers, the patient was referred to us. On admission, the spleen was enlarged 1 cm below the left costal margin. Moreover, the spleen was progressively increased more than 2 cm below the left costal margin when dasatinib was started. Because of increasing splenomegaly, the patient was diagnosed with CML in accelerated phase (AP) [10]. Hematological examination on admission revealed the following: hemoglobin 71 g/l, platelet count 1397×10^9/l, and leukocyte count 64.4×10^9/l, with 6.0 % myelocytes, 5.0 % metamyelocytes, 78.0 % neutrophils, 6.0 % lymphocytes, 1.0 % monocytes, 1.0 % eosinophils and 3.0 % basophils. Her bone marrow was hypercellular, with 4.4 % myeloblasts, 1.2 % promyelocytes, 11.6 % myelocytes, 7.2 % metamyelocytes, 32.0 % neutrophils, 3.6 % lymphocytes, 0.8 % monocytes, 3.2 % eosinophils, 1.6 % basophils, and 34.4 % erythroid precursors. Chromosome analysis of bone marrow cells revealed the karyotype abnormality 46, XX, t(9;22)(q34;q11.2) in all of the metaphases. Analysis of *BCR/ABL* revealed 61.18 % of *ABL* (according to the international scale, IS). Gene mutation analysis of the fusion gene *BCR-ABL1* was negative and her Sokal score was 2.47. Upon admission, glucose metabolism parameters revealed the following: HbA1c fraction 10.9 % (according to National Glycohemoglobin Standardization Program: NGSP), FG 285 mg/dl, and serum C-peptide 1.5 ng/ml (normal range 0.8–2.5). Based on the above findings, the patient was diagnosed as having severe T2D and hemorrhagic gastric ulcers as well as CML in AP.

Initially, the patient received a proton-pump inhibitor for hemorrhagic gastric ulcers, and here T2D was controlled by a diet of 1200 kcal daily and exogenous rapid-acting insulin (average insulin dosage 15 UI/day); median FG level was 170 mg/dl (range 107–275), urine C-peptide level was 15 μg/day (normal range 22.8–155.2). After improvement of gastric ulcers and T2D, the patient received nilotinib (600 mg daily) for CML in AP. After starting nilotinib treatment, the dose of injected rapid-acting insulin was gradually increased to maintain her FG levels (Fig. 1). Ten days after nilotinib treatment, the average dose of rapid-acting insulin was increased to 26 UI daily, whereas urine C-peptide level decreased to 9 μg/day, indicating decreased secretion of endogenous insulin. After twenty-two days of nilotinib treatment, a complete hematological response was obtained; however, on day 31, nilotinib was discontinued because of elevated transaminases, possibly induced by nilotinib. During the discontinuation of nilotinib, FG levels gradually decreased and so the dose of injected rapid-acting insulin was also decreased (Fig. 1). Twelve days after nilotinib discontinuation, FG levels finally decreased to 113 mg/dl (range 64–175), and the average dose of rapid-acting insulin was also decreased to 12 UI/day at plateau phase. Moreover, urine C-peptide level increased to 23.7 μg/day, indicating that discontinuation of nilotinib improved glucose intolerance with increased secretion of endogenous insulin. After 23 days, transaminase levels decreased and nilotinib was re-administered at 400 mg daily. However, 9 days later, FG levels, as well as the required dose of rapid-acting insulin gradually increased (average insulin dosage 15 UI/day) again, and urine C-peptide level decreased (Fig. 1). A complete cytogenetic response (CCyR) was achieved 3 months after the initial treatment with nilotinib. Her T2D has since been well controlled by exogenous insulin therapy.

Discussion

In Japan, there are currently 3 approved BCR-ABL TKIs for newly diagnosed CML patients. For the treatment of this case with CML in AP, we first considered second-generation TKIs, since several randomized studies have clearly demonstrated superior depth of response and improved long-term outcomes with nilotinib and dasatinib therapy compared with imatinib alone [11, 12]. The choice of second-generation TKIs to proceed with should be based on patient comorbidities, since each inhibitor has a distinct side effect profile. In this case, with pre-existing hemorrhagic gastric ulcers and severe T2D, we considered an

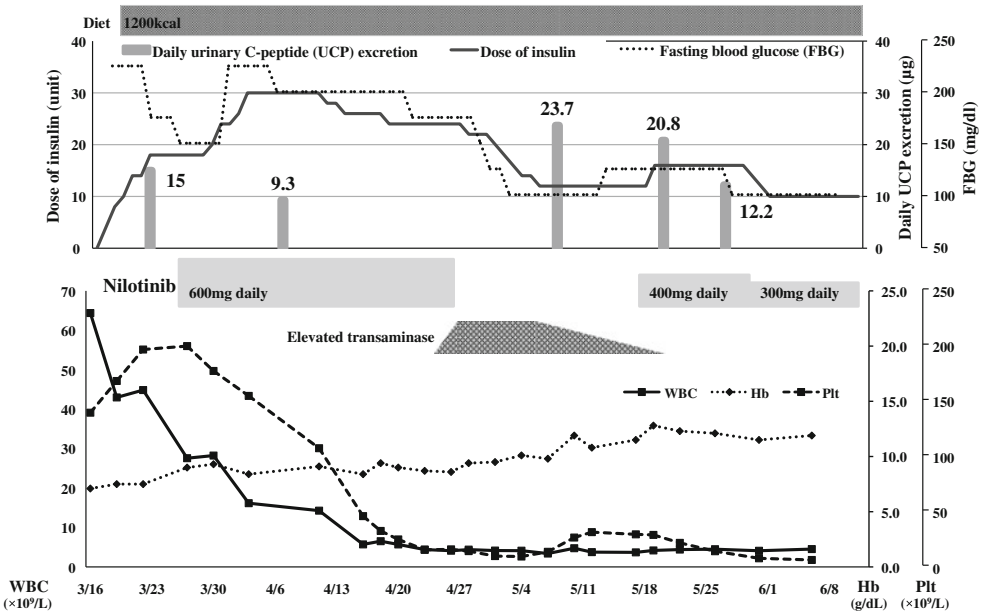

Fig. 1 The Clinical course of the patient with chronic myelogenous leukemia (CML) before and after administration of nilotinib

increased risk of bleeding with dasatinib and an increased risk of hyperglycemia with nilotinib [13]. Moreover, it was reported that administration of proton-pump inhibitor can decrease the absorption of dasatinib from gastrointestinal tract [14]. Since an increased risk of bleeding represented a greater risk of fatality than hyperglycemia, we finally chose nilotinib for the treatment of CML-AP in this case. Subsequently, close attention was required to manage and control the severity of T2D.

There is increasing evidences of the influence of TKIs on glucose handling [15–17]. Among three novel TKIs, several studies have clearly revealed that nilotinib induces hyperglycemia in a subset of non-diabetic and diabetic CML patients [17], whereas imatinib and dasatinib generally do not [15, 16]. In a large, prospective, randomized trial comparing the efficacy of nilotinib with imatinib (The Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients study; ENESTnd), grade 3/4 hyperglycemia occurred in 6 % of patients treated with nilotinib at 300 mg bid, 4 % treated with nilotinib at 400 mg bid, and 0 % treated with imatinib at 400 mg [9]. Of note, no patients treated with nilotinib or imatinib were discontinued from the study because of hyperglycemia, and there were no serious adverse diabetic events. In addition, changes in glucose metabolism parameters, such as HbA1c, FG, insulin, and C peptide, were minimal in patients with pre-existing T2D when treated with imatinib or nilotinib [2]. As a result, they concluded that hyperglycemia induced by nilotinib was usually mild, transient, and manageable [2]. However, CML patients with severe diabetes might have been excluded from the ENESTnd clinical trial. In more advanced diabetic cases, changes in glucose levels as well as glucose metabolism parameters should be promptly clarified, since a fraction of CML patients with severe diabetes may have no other choice than to receive nilotinib in preference to imatinib or dasatinib. Indeed, the comorbidities in this case were exemplary of the need for such clarification.

The mechanisms through which nilotinib induces hyperglycemia remain unknown. In this case of pre-existing severe T2D, we have directly shown that nilotinib altered glucose metabolism by impairing the secretion of endogenous insulin, and this alteration was reversible on discontinuation of nilotinib. The patient successfully gained CCyR after 3 months of nilotinib treatment under the strict control of nilotinib-exacerbated T2D by early intervention with exogenous insulin therapy. Therefore, in CML patients with severe diabetes for whom nilotinib is considered, we strongly recommend sufficient screening of glucose metabolism parameters and early therapeutic intervention with exogenous insulin therapy.

On the other hand, imatinib has been reported to have some potential effects on glucose control [17, 18]. Recent reports suggest possible mechanisms involving enhanced survival of beta cells due to increased activation of anti-apoptotic transcription factor NF-κB or decreased the pro-apoptotic MAPK JNK following imatinib therapy [19]. In other pathways, imatinib can inhibit platelet-derived growth factor (PDGF) receptor signals [20], which may be involved in the pathogenesis of diabetes. In addition, it is possible that imatinib can also inhibit the SCF/c-Kit pathway [21], thereby affecting the inflammatory component of diabetes mellitus [22]. Taken together, these studies indicate that imatinib can counteract diabetes via various molecular mechanisms apart from direct inhibition BCR-ABL as an off-target effect. Originally, nilotinib was

designed as an inhibitor with superior selectivity for BCR-ABL than imatinib. Accordingly, nilotinib may not inhibit NF-κB, MAPK JNK, PDGF, or SCF/c-Kit as imatinib does. Therefore, imatinib might possess the advantage over nilotinib for the treatment of diabetic CML patients in terms of control of blood glucose.

In a conclusion, although the precise mechanisms remain unknown, we have demonstrated that nilotinib treatment for patients with severe T2D might induce reversible decreased secretion of endogenous insulin, but does not represent an obstacle to CML treatment. Therefore, based on our observations, we highly recommend screening and close monitoring of diabetic parameters before and during nilotinib therapy, and early intervention with exogenous insulin therapy if necessary.

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Conflict of interest None.

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