Rapid Amelioration of Hyperglycemia Facilitated by Dasatinib in a Chronic Myeloid Leukemia Patient with type 2 Diabetes Mellitus

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Abstract
Tyrosine kinase inhibitors (TKIs) have been shown to affect glucose metabolism in patients with chronic myeloid leukemia (CML); however, their precise mechanism of action remains unknown. We herein report the case of a 57-year-old diabetic CML patient who was resistant to imatinib and initially required 20 units of insulin daily to control his blood glucose levels. After the initiation of dasatinib, the patient’s insulin requirements declined rapidly and insulin treatment was discontinued within two weeks. Meanwhile, the fasting C-peptide immunoreactivity increased two-fold, suggesting that dasatinib facilitated the recovery of insulin production. Dasatinib may therefore be beneficial for diabetic CML patients, especially those who require insulin treatment.

Key words: type 2 diabetes mellitus, tyrosine kinase inhibitors, chronic myeloid leukemia, insulin secretion, insulin sensitivity

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Introduction
Tyrosine kinase inhibitors (TKIs) such as imatinib, nilotinib, and dasatinib, have been shown to affect glucose metabolism in some patients with chronic myeloid leukemia (CML). In the clinical setting, both imatinib and dasatinib may ameliorate the fasting glucose level (1-4), but nilotinib may worsen it (5). Although the mechanisms responsible for the conflicting action of TKIs on blood glucose levels remain unknown, the selection of TKIs should be carefully considered in CML patients with diabetes. We herein report the case of a rapid amelioration of hyperglycemia by dasatinib in an accelerated-phase CML patient with type 2 diabetes mellitus.

Case Report
A 57-year-old male patient with accelerated-phase CML was admitted to NTT West Kyushu Hospital for treatment of his hyperglycemia in January 2011. Since being diagnosed with chronic-phase CML in 1990, he had been treated with various anti-CML drugs such as busulfan, hydroxyurea, interferon alpha (IFN-α), and imatinib. He was resistant to these therapies, showing no cytogenetic response; therefore, he was enrolled in a clinical trial of bosutinib in 2009 at Kumamoto University Hospital. Although a minimum cytogenetic response was achieved, bosutinib was discontinued because of severe anemia and thrombocytopenia (Grade 3 for both with respect to the Common Terminology Criteria for Adverse Events, version 4.0). Thereafter, he required frequent red blood cell transfusions (a total of 72
units during 15 months) and finally progressed to the accelerated phase. His postprandial blood glucose levels had been stable without any medication at 130-160 mg/dL with HbA1c [National Glycohemoglobin Standardization Program (NGSP)] 6.2-6.6% (6) until symptoms such as thirst and malaise occurred with hyperglycemia (635 mg/dL) just before his admission. The laboratory findings on admission showed leukocytosis (white blood cell count 39,000/μL) with 68% basophils, moderate anemia (Hb 7.2 g/dL), thrombocytopenia (platelet count 5.3×10⁴/μL), an elevated serum ferritin level (3,053.9 ng/dL), severe hyperglycemia (fasting blood glucose level 299 mg/dL, HbA1c level 12.0%, glycated albumin level 60.0%), and low levels of C-peptide immunoreactivity in his serum and urine (Table).

Because his dietary habits had not changed, we speculated that he might have been suffering from hyperferritinemia associated with the progression of type 2 diabetes via secondary hemochromatosis. Therefore, we immediately started insulin injection therapy with the oral iron-chelating agent deferasirox. During the first three weeks of hospitalization, approximately 20 units daily of insulin aspart and insulin detemir were required to control his blood glucose levels (Fig. 1). Low-dose dasatinib (50 mg daily) was then initiated for the treatment of progressive basophilic leukocytosis. A favorable hematological response to dasatinib was achieved, with the disappearance of basophilia two weeks after starting dasatinib (Fig. 1). Interestingly, in parallel with the hematological response, diabetes markers such as the fasting plasma glucose (FPG) and HbA1c were also rapidly ameliorated despite the fact that the serum ferritin level remained high (Fig. 1). We were able to stop insulin administration to the patient after five weeks of hospitalization.

Table. Laboratory Findings on Admission

<table>
<thead>
<tr>
<th>Blood Cell Count</th>
<th>Blood Chemistry</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 39800/μL</td>
<td>TP 7.2</td>
<td>CRP 1.52 mg/dL</td>
</tr>
<tr>
<td>Ba 68 %</td>
<td>Alb 3.2</td>
<td>Ferritin 3053.9 ng/mL</td>
</tr>
<tr>
<td>Eo 3 %</td>
<td>T-Bil 1.1</td>
<td>C-peptide (NGSP) 12.0 mg/dL</td>
</tr>
<tr>
<td>Pro 1 %</td>
<td>AST 10</td>
<td>Glycated albumin 60.0 %</td>
</tr>
<tr>
<td>My 1 %</td>
<td>ALT 8</td>
<td>Anti GAD−Ab &lt;0.3 U/mL</td>
</tr>
<tr>
<td>Met 1 %</td>
<td>ALP 173</td>
<td>Serum CPR** 0.90 ng/mL</td>
</tr>
<tr>
<td>St 5 %</td>
<td>LDH 333</td>
<td>Urinary CPR 54.8 μg/day</td>
</tr>
<tr>
<td>Sgg 12 %</td>
<td>γGTP 19</td>
<td></td>
</tr>
<tr>
<td>Ly 8 %</td>
<td>CPK 12</td>
<td></td>
</tr>
<tr>
<td>Mo 1 %</td>
<td>T-Chol 117</td>
<td></td>
</tr>
<tr>
<td>RBC 238×10⁶/μL</td>
<td>TG 116</td>
<td></td>
</tr>
<tr>
<td>Hb 7.2 g/dL</td>
<td>BUN 18.7</td>
<td></td>
</tr>
<tr>
<td>Ht 21.9 %</td>
<td>Cre 0.6</td>
<td></td>
</tr>
<tr>
<td>MCV 92.0 fl</td>
<td>UA 4.6</td>
<td></td>
</tr>
<tr>
<td>MCH 30.3 pg</td>
<td>Na 135</td>
<td></td>
</tr>
<tr>
<td>MCHC 32.9 %</td>
<td>K 4.4</td>
<td></td>
</tr>
<tr>
<td>Plt 5.3×10⁵/μL</td>
<td>Ca 9.4</td>
<td></td>
</tr>
</tbody>
</table>

*FPG: fasting plasma glucose, GAD: glutamic acid decarboxylase, ""CPR: C-peptide immunoreactivity

Figure 1. Clinical course. Daily dose of insulin and absolute basophil counts were plotted after admission in the upper and lower panels, respectively. Dasatinib was started at 3 weeks of hospitalization.

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(Figs. 1 and 2). The C-peptide immunoreactivity was sufficiently recovered from 0.9 ng/mL and 54.8 μg/day to 1.75 ng/mL and 85.6 μg/day in blood and urine, respectively, after dasatinib treatment (Fig. 1), thus suggesting that the agent had ameliorated the dysfunction of insulin secretion in the patient.

Because his evening postprandial plasma glucose levels remained relatively high (200-240 mg/dL) after discontinuation of the insulin regimen, we prescribed an oral hypoglycemic agent (glimepiride, 1 mg daily). After 10 months of dasatinib treatment, the drug remained well tolerated and the favorable glucose metabolism was maintained (postprandial blood glucose level 145 mg/dL, HbA1c level 6.4%, glycated albumin level 19.4%).

**Discussion**

Second-generation TKIs such as dasatinib and nilotinib have been developed to overcome resistance to imatinib and are now approved for use in the treatment of not only imatinib-resistant or -intolerant patients, but also newly diagnosed patients with CML. Although both of the second-generation TKIs possess potent inhibitory activity for breakpoint cluster region-Abelson (BCR-ABL) in comparison to imatinib, they act on different target molecules: nilotinib is more selective for BCR-ABL and dasatinib strongly inhibits SRC family kinases. This functional difference between the two agents may lead to varying adverse reactions: e.g., elevations of plasma lipase and blood glucose levels are occasionally observed during nilotinib therapy; in contrast, pleural effusion is associated with dasatinib treatment. Understanding these features is helpful for clinical decision-making in the selection of second-generation TKIs (i.e., dasatinib or nilotinib), especially for patients who have comorbidities such as diabetes mellitus and pancreatitis. In the present case, we selected dasatinib for the treatment of imatinib-resistant CML in order to avoid any worsening of the patient’s diabetes. Unexpectedly, his glucose metabolism rapidly improved soon after the initiation of treatment with dasatinib, thus resulting in an amelioration of the insulin requirement, followed by recovery of intrinsic insulin secretion after a few weeks of dasatinib treatment (Fig. 1). There was no change in the patient’s food intake or medications before or after the introduction of dasatinib. In addition, his serum ferritin levels were not significantly decreased following treatment with the iron-chelating agent, even after the discontinuation of insulin (Fig. 1). These clinical findings suggest that the rapid improvement in glucose metabolism may have been specifically associated with an effect of dasatinib in our patient, although we could not exclude the possibility of a CML-related worsening of the patient’s glucose metabolism.

An effect of TKIs on glucose metabolism was initially demonstrated with imatinib therapy for CML in 2004 (1, 2). Thereafter, other TKIs such as sunitinib, dasatinib, sorafenib, and pazopanib have been reported to have similar effects to imatinib in patients with various malignant diseases (3, 4, 7). The literature suggests that in most cases of TKI treatment, pre-existing diabetes mellitus is ameliorated or the average blood glucose levels are decreased to some extent. Similarly, in this case, dasatinib treatment rapidly and completely ameliorated the requirement for insulin.

The mechanism of action of imatinib on the glucose metabolism has been extensively analyzed. Imatinib was initially examined for an inhibitory effect on apoptosis of pancreatic β cells, which is one of the major causes of diabetes. Imatinib protected human β cells from chemical-induced apoptosis in vitro through inhibition of c-ABL and successive activation of nuclear factor-kappa B (NFκB) (8). In non-obese diabetic mice, an animal model of type 1 diabetes, the oral administration of imatinib decreased the incidence of overt diabetes, likely because of its inhibitory effect on the platelet-derived growth factor receptor (PDGFR) tyrosine kinase, which is crucial for the induction of β-cell apoptosis, which leads to diabetes (9). In addition to the direct effect of imatinib on pancreatic β cells, imatinib has

**Figure 2.** Daily profiles of blood glucose levels before and after treatment with dasatinib.
been shown to ameliorate insulin resistance in peripheral tissues. In diabetic rats fed a high-fat diet, imatinib improved the insulin sensitivity and glucose disposal rates (10). The amelioration of insulin resistance may be associated with the imatinib-mediated inhibition of tumor necrosis factor alpha (TNF-α) production (11) and/or a decrease in endoplasmic reticulum stress (12).

It is unclear whether the favorable effect of dasatinib on glucose metabolism reported here can be explained by mechanisms similar to those proposed for imatinib. The inhibition of c-ABL and PDGFR have been suggested as a possible mechanism, because these molecules are common targets for both imatinib and dasatinib. However, this suggestion is still controversial because nilotinib, a potent inhibitor of c-ABL and PDGFR, exerts an opposing action to that elicited by imatinib or dasatinib, in terms of the effects on glucose metabolism. Recently, SRC kinase, a molecular target for dasatinib, has been shown to be associated with the regulation of insulin production in β cells. Ceng et al. reported that augmented activity of SRC kinase decreased insulin secretion in cultured human β cells even at elevated intracellular Ca$^{2+}$ levels, while the inhibition of SRC kinase activity with TKIs enhanced the insulin release in a Ca$^{2+}$-concentration-dependent manner (13). On the other hand, Kominato et al. found that a selective SRC inhibitor, 4-amino-5- (4-chlorophenyl)-7- (t-butyl) pyrazolo [3,4-d] pyrimidine (PP2) significantly decreased high glucose-induced reactive oxygen species (ROS) production in diabetic Goto-Kakizaki rat-derived islet cells compared with normal control cells. This suggests that SRC kinase may be activated under diabetic conditions, leading to an elevation of ROS production when islet cells are exposed to high glucose levels. Because ROS are one of the most important factors that impair insulin secretion in β cells, it is suggested that the suppression of SRC kinase activity decreases ROS production, and may thus improve insulin secretion in diabetics (14). The results of these studies suggest a possible interaction between the dasatinib-induced SRC inhibition and the rapid recovery of endogenous insulin production in the present patient. Interestingly, this patient’s diabetes did not worsen during treatment with bosutinib, another BCR-ABL/SRC dual kinase inhibitor.

After the great success of molecular-targeting therapy for CML, numerous TKIs have been developed and used for the clinical treatment of various types of neoplasms. It is important to take into account the effects of TKIs on glucose metabolism during TKI therapy, particularly in diabetic patients. Interestingly, some tyrosine kinases, including SRC, appear to be potential targets for the development of a new class of anti-diabetic agents. Further investigations are therefore needed to clarify the mode of action of TKIs in relation to the glucose metabolism.

The authors state that they have no Conflict of Interest (COI).

Tatsuya Kawaguchi and Keiko Ono are equally contributed to this work.

References