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Invited review

How tyrosine kinase inhibitors impair metabolism and endocrine system function: A systematic updated review

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ABSTRACT

Tyrosine kinase inhibitors (TKIs) advent has deeply changed the outcome of chronic myeloid leukemia (CML) patients, with improved rates of response and overall survival. However, for this success some patients paid the price of a number of peculiar side effects, the so-called off-target side effects, specific for each one TKI. These effects are due to non-selective inhibition of other tyrosine kinase receptors, such as PDGFR, c-KIT, Src, VEGF. Consequences of this inhibition, some metabolic changes during the treatment with TKIs are reported. Aim of present review is to report metabolic changes and potential mechanisms involved in the pathogenesis related to imatinib, second (nilotinib and dasatinib) and third generation (bosutinib and ponatinib) TKIs.

Contents

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1. Introduction

Chronic myeloid leukemia (CML) is a clonal disorder resulting from the malignant transformation of a pluripotent stem cell harboring the Philadelphia chromosome (Ph), a genetic abnormality which arises from a reciprocal translocation, t(9;22) (q34;q11) [1–6]. This rearrangement fuses the genes encoding for BCR and ABL, resulting in the expression of the constitutively active protein tyrosine kinase, *BCR-ABL1*. The pivotal role of *BCR-ABL1* in the pathogenesis of CML provided the rationale for designing inhibitory agents specifically targeting the constitutive tyrosine kinase activity. Imatinib mesylate (IM) is an inhibitor of ABL1, *BCR-ABL1* and other tyrosine kinases [7]. IM provides effective and durable therapy for CML: 8-year follow-up of the phase III International Randomized IFN vs STI571 (IRIS) study, showed 85% overall survival (OS) rates, but reported that 30% of patients had unfavorable outcomes, mostly due to primary (17%) or acquired resistance (15%) [8,9]. Hence, second generation TKIs (dasatinib and nilotinib) were introduced in the pharmacological armamentarium successfully rescuing about 50% of IM-resistant patients [10,11]. Currently, dasatinib and nilotinib can also be prescribed in the first-line setting after the results of DASISION and ENESTnd randomized phase III trials [12,13]. Third generation TKIs (bosutinib and ponatinib) are actually approved for resistant or intolerant patients to previous lines of therapy, potentially active against BCR-ABL1 and other tyrosine kinase [14,15]. Due to non-selective action, all these drugs have several side effects related to the inhibition of other tyrosine kinases, such as c-kit, PDGFR, Src or EPHB4. Metabolic class effects were reported, which identified specifically the safety profile of each drug tested against CML. Aim of this review is to summarize principal metabolic changes induced by imatinib, second- or third-generation TKIs, discuss potential pathogenetic mechanisms and suggest appropriate management.

2. Glucose metabolism

2.1. Imatinib

Imatinib mediates changes in glucose metabolism: several in vitro evidences have reported the control of glucose substrate flux as antiproliferative action mediated by the drug in BCR-ABL positive cells. One of the first in vitro evidences showed that imatinib treatment might restrict de novo nucleic and fatty acid synthesis by inducing fall in hexokinase and glucose-6-phosphate 1-dehydrogenase activities and also by altering pathway of carbon flux in the pentose cycle in myeloid tumor cells [16].

Glucose metabolism was tested in BCR-ABL positive cells exposed to imatinib. CML-T1 and K562, two human BCR-ABL positive cell lines and HC-1, a BCR-ABL negative cell line were incubated for 96 h with different concentrations of imatinib. Glucose metabolism, energy state and changes in endogenous metabolites after incubation with imatinib were tested by magnetic resonance spectroscopy. No metabolic changes were observed in BCR-ABL1 negative cells, whereas in BCR-ABL positive cells, concentrations of imatinib 0.1–1.0 mol/L decreased glucose uptake from the media by suppressing glycolytic cell activity and increasing mitochondrial Krebs cycle activity. Increased energy state was the consequence of improvement in mitochondrial glucose metabolism: imatinib could reverse the Warburg effect (mitochondrial metabolism impaired and glycolysis elevated) [17]. Apoptosis was observed when the drug was used at higher concentrations, proved by increased concentrations of glycerophosphocholine, a marker of the membrane degradation process. Therefore, imatinib may act as antiproliferative drug controlling glucose substrate flux: in fact, BCR-ABL positive cells express high affinity GLUT-1 glucose transporter and demonstrate increased glucose uptake. In vitro, imatinib led to the internalization of 90% GLUT-1 transporter and drastically decreased hexose uptake [18]. In vitro stable isotope-based dynamic metabolic profiling (SIDMAP) studies, that involved myeloid cells isolated from patients who developed resistance against imatinib, indicated that non-oxidative ribose synthesis from glucose and decreased mitochondrial glucose oxidation are significant metabolic signatures of drug resistance and disease progression [19]. There is also evidence that imatinib-resistant cells utilize alternate substrates for macromolecule synthesis to overcome limited glucose transport controlled by imatinib. Using nuclear magnetic resonance spectroscopy and gas chromatography mass spectrometry in sensitive K562-s and LAMA84-s BCR-ABL-positive cells, to assess (13)C glucose uptake and metabolism during imatinib, showed that these lines have decreased glucose uptake, decreased lactate production, and an improved oxidative TCA cycle. Indeed, resistant K562-r and LAMA84-r cells maintained a highly glycolytic metabolic phenotype with elevated glucose uptake and lactate production; alternative RNA synthesis via the non-oxidative transketolase pathway was increased in imatinib-resistant cells. Intracellular translocation of GLUT-1 from the plasma membrane into the intracellular fraction was observed in sensitive cells treated with imatinib, whereas GLUT-1 remained located at the plasma membrane in resistant cell lines [20]. Therefore, specific metabolic markers for imatinib-resistance were identified including increased glycolytic activity and phospholipid turnover [21].

Kluza et al. explored mitochondrial dysfunction as potential metabolic alterations of imatinib-resistant leukemic cells: expression of key glycolytic enzymes, at least partly mediated by HIF-1α, was modified in imatinib-resistant cells suggesting that imatinib-resistant cells uncouple glycolytic flux from pyruvate oxidation. Interestingly, mitochondria of imatinib-resistant cells exhibited accumulation of TCA cycle intermediates, increased NADH and low oxygen consumption and, consequently, mitochondria generate more reactive oxygen species (ROS) [22].

In vivo reports were concordant that imatinib improves fasting glucose in diabetic patients with consequent reduction of oral antidiabetic drugs or insulin dosage.

In 2004, our group [23] reported for the first time on 7 diabetic CML patients treated with imatinib, diagnosed as diabetic at least 10 years before the diagnosis of CML. Four patients were in chronic phase, whereas 3 patients were in accelerated phase and were treated with 600 mg/day of imatinib: all patients but one were resistant to prior interferon therapy. In 6 of them, we did observe an improvement of fasting glucose level (FG), and a consequent reduction of oral antidiabetic drugs or insulin administration. Maintaining the same lifestyle and diet, median FG level changed from 220 mg/dl at baseline (range 162–305 mg/dl) to 108 mg/dl (range 89–124 mg/dl) at 12 months. Only one patient in accelerated phase, who was resistant to imatinib after 1 year of therapy, did not obtain a control of FG despite increasing insulin administration.

We reported then another case [24] in which we sequentially tested the glycosylated hemoglobin fraction (HbA1C) and plasma insulin: indirect effects on increased insulin sensitivity were proven by the progressive reduction of HbA1C fraction and the demonstration of stable insulin plasma level.

After our first description, Veneri et al. described a diabetic CML patient who soon after imatinib therapy achieved a complete cytogenetic remission (CCR) and a control of diabetes, in the absence of alimentary habits modifications [25].

Differently from what reported previously, Dingli and colleagues described 9 diabetic patients treated with imatinib without specific effect on glycaemic control. It has to be considered, however, that patients were affected by different diseases (4 patients had CML, 2 had GIST and 3 patients were treated for