Pancreatic enzymes elevation in chronic myeloid leukemia patients treated with nilotinib after imatinib failure

by Francesca Palandri, Fausto Castagnetti, Simona Soverini, Angela Poerio, Gabriele Gugliotta, Simona Luatti, Marilina Amabile, Giovanni Martinelli, Gianantonio Rosti, and Michele Baccarani

Haematologica 2009 [Epub ahead of print]

doi:10.3324/haematol.2009.010496

Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. This paper will now undergo editing, proof correction and final approval by the authors. Please note that during this production process changes may be made, and errors may be identified and corrected. The final version of the manuscript will appear both in the print and the online journal. All legal disclaimers that apply to the journal also pertain to this production process.

Haematologica (pISSN: 0390-6078, eISSN: 1592-8721, NLM ID: 0417435, www.haematologica.org) publishes peer-reviewed papers across all areas of experimental and clinical hematology. The journal is owned by the Ferrata Storti Foundation, a non-profit organization, and serves the scientific community with strict adherence to the principles of open access publishing (www.doaj.org). In addition, the journal makes every paper published immediately available in PubMed Central (PMC), the US National Institutes of Health (NIH) free digital archive of biomedical and life sciences journal literature. Haematologica is the official organ of the European Hematology Association (www.ehaweb.org).

Support Haematologica and Open Access Publishing by becoming a member of the European Hematology Association (EHA) and enjoying the benefits of this membership, which include free participation in the online CME program.
Pancreatic enzymes elevation in chronic myeloid leukemia patients treated with nilotinib after imatinib failure

Francesca Palandri, Fausto Castagnetti, Simona Soverini, Angela Poerio, Gabriele Gugliotta, Simona Luatti, Marilina Amabile, Giovanni Martinelli, Gianantonio Rosti, and Michele Baccarani

Department of Hematology and Medical Oncology “L. and A. Seràgnoli” St. Orsola-Malpighi University of Bologna, Bologna

ABSTRACT

An increase in the serum concentration of pancreatic enzymes (amylase and lipase) was reported in a proportion of imatinib-resistant and/or intolerant Philadelphia-positive chronic myeloid leukemia (CML) patients treated with nilotinib. Acute pancreatitis was very rare, and the relevance of these laboratory alterations remains unknown. We report on 8 CML patients who developed serum lipase/amylase elevation during treatment with Nilotinib. After a median follow-up of 26 months, none of these patients developed an acute pancreatitis or clinical signs of pancreatic disease. Pancreatic hyperenzymemia never led to permanent drug discontinuation and required Nilotinib temporary interruption in one case only. The median cumulative duration of dose interruptions and response to treatment were comparable in patients with or without pancreatic enzyme elevation. The mechanisms of action of nilotinib on pancreatic enzymes deserves to be investigated: however, in our experience, the relevance of pancreatic hyperenzymemia was clinically very limited.

Key words: hyperlipasemia, hyperamylasemia, pancreatic enzymes, chronic myeloid leukemia, imatinib, nilotinib

Design and Methods

Patients were enrolled between June 2005 and February 2008 in two studies sponsored by Novartis Pharmaceuticals (registered at www.clinicaltrials.gov under NCT00384228 and NCT00802016). The studies were conducted in accordance with the Declaration of Helsinki. Both studies were approved by the ethic committee of the St. Orsola-Malpighi University Hospital and all patients gave written informed consent according to institutional guidelines. Enrolment criteria have been described elsewhere.4 Briefly, patients with imatinib-resistant or intolerant CML in chronic phase, accelerated phase and blast crisis who were at least 18 years old were eligible if they had adequate performance status (World Health Organization Performance Score ≤2), and normal hepatic, renal, and cardiac functions. Nilotinib starting dose was 400 mg twice daily for all patients. Blood counts and bio-

Acknowledgments: the skilful assistance of Irina Mantovani is gratefully acknowledged. Funding: the study was supported by European LeukemiaNet funds, the Italian Association for Cancer Research (A.I.R.C.), COFIN, and BolognAIL.. Manuscript received on April 24, 2009. Revised version arrived on June 1, 2009. Manuscript accepted on June 15, 2009. Correspondence: Francesca Palandri, MD. Department of Hematology and Medical Oncology “L. and A. Seràgnoli”, St. Orsola-Malpighi University Hospital, Via Massarenti, 9, 40138 Bologna, Italy. E-mail: francesca.palandri@libero.it
chemistries were obtained weekly for the first 8 weeks, and thereafter every 2 weeks. Cytogenetic studies on bone marrow samples were performed with conventional cytogenetic analysis at baseline and at 3-6 month intervals thereafter. The cytogenetic response was rated according to European LeukemiaNet guidelines. Safety assessments included evaluation of adverse events, hematologic and biochemical testing, urinalysis, cardiac enzyme assessment, serial electrocardiogram evaluation, and physical examination. Amylase and lipase concentrations were measured at the central laboratory of our hospital. The normal reference range is 20-110 IU/L for amylase and 13-55 IU/L for lipase. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

Results

Patients
A total of 37 CML patients intolerant or resistant to imatinib were enrolled in the studies. Nineteen were male and 18 female. Median age at CML diagnosis was 49 years (range, 12-71); median interval between CML diagnosis and nilotinib start was 48 months (range, 4-266). Twenty-four patients were in chronic phase, 4 in accelerated phase and 9 in blast phase (4 lymphoid and 5 myeloid blast phase). Nilotinib was initiated because of imatinib-resistance in 30 patients (81%). In the remaining 7 imatinib-intolerant patients, reasons for imatinib discontinuation were: fluid retention (4 patients), skin reactions (1), hematological toxicity (2). Median follow-up of living patients was 29 months (range, 9-42).

Incidence and severity of pancreatic enzymes elevations

Lipase and amylase serum levels have been performed in all patients every 1 to 3 months, according to protocol’s requirements and to medical indications, during the entire course of nilotinib therapy. Serum fasting glucose levels were normal and no signs of malabsorption were ever recorded. Therefore, pancreatic function tests were neither required nor performed. During the course of nilotinib therapy, 8 patients (21.6%) showed increased lipase and/or amylase levels (Table 2). Seven patients were in chronic phase and one in accelerated phase. Median age at nilotinib start was 51 years (range, 36-68); 6 were male and 2 female. The median interval between Nilotinib start and lipase/amylase elevation was 3 months (range, 7 days-30 months). Lipase elevation was detected as single alteration in 5 patients, while a transient amylase elevation was concomitantly detected in two patients. One patient experienced isolated serum amylase elevation grade 2. Overall, in 5 cases (13.5%) serum lipase increase was grade 3 (from 2 to 5 times over the upper normal limit), whereas all amylase elevations were grade 2 (from 1.5 to 2 times over the upper normal limit). Pancreatic enzymes increase presented as single isolated elevated values or as transient episodes in all cases, with the exception of patient MB, who experienced frequent recurrences of hyperoenzymemia. During treatment, all patients had

Table 1. Clinical and laboratory features of the 8 patients with pancreatic enzymes elevation during nilotinib therapy.

<table>
<thead>
<tr>
<th>Pt (sex)</th>
<th>Age (yrs)</th>
<th>Disease status</th>
<th>Previous therapies</th>
<th>Causes of IM discontinuation</th>
<th>Lipase increase grade 2</th>
<th>Lipase increase grade 3</th>
<th>Amylase increase grade 2</th>
<th>Enzyme elevation at last follow-up</th>
<th>Therapy at last contact</th>
<th>Status at last follow-up</th>
<th>Follow-up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA (M)</td>
<td>51</td>
<td>CP</td>
<td>IM resistance</td>
<td>1a</td>
<td>93</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>Nilo 400 mg BID1</td>
<td>alive</td>
<td>CCgR</td>
</tr>
<tr>
<td>GV (M)</td>
<td>68</td>
<td>AP</td>
<td>IM resistance</td>
<td>1</td>
<td>90</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>Nilo 400 mg BID1</td>
<td>alive</td>
<td>CCgR</td>
</tr>
<tr>
<td>AS (M)</td>
<td>47</td>
<td>CP</td>
<td>IFN, IM,</td>
<td>adverse event (skin)</td>
<td>0</td>
<td>NA</td>
<td>2b</td>
<td>52</td>
<td>NA</td>
<td>Nilo 400 mg BID2</td>
<td>alive</td>
</tr>
<tr>
<td>AP (F)</td>
<td>43</td>
<td>CP</td>
<td>IM</td>
<td>adverse event (neutropenia)</td>
<td>0</td>
<td>NA</td>
<td>1c</td>
<td>15</td>
<td>NA</td>
<td>Nilo 400 mg BID2</td>
<td>alive</td>
</tr>
<tr>
<td>PG (F)</td>
<td>36</td>
<td>CP</td>
<td>IM, dasatinib</td>
<td>resistance</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>12</td>
<td>NA</td>
<td>Nilo 400 mg OAD4</td>
<td>alive</td>
</tr>
<tr>
<td>PD (M)</td>
<td>54</td>
<td>CP</td>
<td>IM</td>
<td>resistance</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>180</td>
<td>yes (amylase) grade 1</td>
<td>Nilo 400 mg OAD5</td>
<td>alive</td>
</tr>
<tr>
<td>MG (M)</td>
<td>51</td>
<td>CP</td>
<td>IFN, IM</td>
<td>resistance</td>
<td>1</td>
<td>19</td>
<td>1</td>
<td>7</td>
<td>27</td>
<td>Nilo 400 mg OAD5</td>
<td>alive</td>
</tr>
<tr>
<td>MB (M)</td>
<td>51</td>
<td>CP</td>
<td>IFN, ASCT</td>
<td>resistance</td>
<td>1</td>
<td>15</td>
<td>6^</td>
<td>510</td>
<td>5</td>
<td>Nilo 400 mg OAD4</td>
<td>alive</td>
</tr>
</tbody>
</table>

a) concomitant to grade 2 increased serum gamma-glutamyl transpeptidase. b) concomitant to grade 2 diarrhea. c) concomitant to grade 2 skin rash. d) concomitant to grade 2 increased serum bilirubin. e) concomitant drugs: 1) alfuzosin, allopurinol, atenolol. 2) acetylsalicylic acid, metoprolol. 3) furosemid, lorazepam. 4) omeprazole. 5) alfuzosin, allopurinol. 6) including 4 episodes grade 4. CP: chronic phase. AP: accelerated phase. IM: imatinib. IFN: interferon-α. alloHSCT: allogeneic hematopoietic stem cell transplant. ASCT: autologous stem cell transplant. NA: not applicable. CCgR: complete cytogenetic response.
maintained the same lifestyle and alimentary habits; in particular, alcohol abuse was excluded in all cases. Concomitant drugs were also recorded (Table 2), but none of them seemed to be related to pancreatic hyperenzymemia.

Clinical implications of pancreatic enzymes elevations

In all these subjects, the hyperenzymemia was discovered incidentally when tests for pancreatic enzymes were carried out as a part of a routine work-up. None of these patients was diabetic, nor presented a history positive for gastrointestinal diseases, including gallstones, biliary duct occlusions, pancreatitis, hepatitis. At the first evidence of enzyme elevation, all patients were studied with abdominal ultrasonography, which resulted normal in all cases. Other concomitant AEs were recorded and are listed in Table 1. Impaired renal function was also excluded. None of the patients developed acute pancreatitis. Patient MB presented a serum lipase increase grade 3 at baseline evaluation; an abdominal computed tomography (CT) excluded pancreatic pathoanatomic anomalies before Nilotinib start. In this patient, pancreatic enzymes showed a fluctuating behaviour; the phenomenon was monitored with a 15-days clinical and laboratory tests, and was investigated with 3 computed tomography scan and 1 MRCP (magnetic resonance colangio-pancreatography), all of which failed to reveal abdominal anatomic alterations. Endoscopic retrograde pancreatography and exocrine pancreatic function study by the secretin-cerulein test were not performed because potentially hurtful, in absence of clinical signs of pancreatic disease. At last follow-up, 42 months after Nilotinib start, the patient is alive and well, in continuous, Nilotinib-induced complete cytogenetic response, and in ongoing therapy with Nilotinib at reduced dosage (400 mg daily) (Figure 1).

Overall, Nilotinib dose was reduced to 400 mg daily in four patients, because of pancreatic hyperenzymemia (patients MB and MG), recurrent thrombocytopenia (patient PG) and gastric intolerance (patient PD). Only patient MG discontinued Nilotinib for 26 days because of hyperenzymemia; the median cumulative duration in days of dose interruptions was similar in CP-CML patients with or without pancreatic enzyme elevations (19 days, range 0-50, versus 1 days, range 0-146, respectively, p=0.25). The proportion of complete cytogenetic responders was also comparable in the two groups: among the 7 CP-CML patients with pancreatic hyperenzymemia, 6 achieved a complete cytogenic response (versus 9 complete responders out of 17 chronic phase patients without enzyme elevation, p=0.19).

Discussion and Results

Pancreatic enzymes elevation was reported as an unexpected adverse event in CML patients treated with nilotinib after imatinib failure. Among the 119 CML patients treated with Nilotinib in accelerated phase, 18% and 2% of the patients experienced a grade 3-4 increase in lipase and amylase levels, respectively, with one patient developing acute pancreatitis after a median duration of treatment of 6.7 months.7 Grade 3-4 elevation of serum lipase levels was also recorded in 14% of 318 CML patients treated with nilotinib in chronic phase, and acute pancreatitis was reported in 3 cases (1%), with a median duration of exposure of 8 months.6,4

The reason for pancreatic enzymes elevation is unknown. One mechanism may be due to the capability of nilotinib to inhibit with high affinity the non-receptor tyrosine kinase c-Abl. Besides the kinase domain, the c-Abl protein interacts with signalling proteins, nucleo-cytoplasmic shuttling, DNA and actin binding sites, thus integrating information from multiple pathways in different cellular compartments.10 Therefore, it is possible that c-Abl inhibition might interfere with the molecular mechanisms regulating pancreatic cells death, inducing a pancreatic damage. Another possibility is that the drug may act on unknown intracellular pathways involved in Calcium release from the intracellular acinar stores, which regulates exocrine pancreatic secretion or may promote the accumulation of fatty acid inside the pancreatic acinar cell, which disturbs exocytosis.14 However, pancreatic enzymes elevations are rarely observed during exposure to other ABL kinase inhibitors, and the molecular mechanisms of action of nilotinib on pancreatic enzymes level deserves to be investigated. However, defining and controlling the clinical implications of the side effects of a new oncology drug is particularly important and challenging, considering the gravity of the disease and the potential therapeutic effect. An increase in serum concentration of pancreatic enzymes is usually an expression of pancreatic disease; however, several conditions can be responsible for elevated amylase and/or lipase levels, which may also be a non-specific phenomenon without any clinical implication.16,17 Particularly, benign pancreatic hyperenzymemia (BPH)18 is a syndrome characterized by pancreatic enzymes elevations persisting over time with consider-
able fluctuations, in the absence of pancreatic disease, condition very similar to that observed in patient MB (Figure 1).

Regular monitoring and prolonged observation are needed to establish whether pancreatic enzyme elevations during nilotinib therapy are a benign laboratory abnormality or a serious adverse event reflecting a (potential) pancreatic disease. In our experience, with a median observation time longer than 2 years, these alterations were short-lasting and self-limiting, requiring preventative temporary drug discontinuation in one patient only. None of the patients required permanent treatment interruption due to pancreatic enzyme elevation and nilotinib dose was precautionary reduced in two cases only. More importantly, no patient developed acute pancreatitis or clinical signs of pancreatic disease, like pancreatic-type pain, obstructive jaundice, maldigestion, diabetes, pancreatic cysts and ascites.

**References**


**Authorship and Disclosures**

GR, GM, MB: conception and design; FC, GG, SS, AP, SL, MA, GM; provision of study materials or patients; collection and assembly of data: FC; data analysis and interpretation: FP, GR, MB; manuscript writing: FP, GR, MB; final approval of manuscript: MB.

Consultant or Advisory Role: GM: Novartis (C), Bristol-Myers Squibb Co (C); GR: Novartis (C), Bristol-Myers Squibb Co (C); MB: Novartis (C)

Honoraria: Michele Baccarani, Novartis Pharma.