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

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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 patients treated with nilotinib. Acute pancreatitis was very rare, and the relevance of these laboratory alterations remains unknown. We report on 8 chronic myeloid leukemia 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.

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Introduction

Thanks to its striking effectiveness, imatinib (IM) (Glivec, Gleevec; Novartis Pharmaceuticals, NJ), a Bcr-Abl tyrosine kinase inhibitor (TKI), has rapidly become the standard front-line treatment of Philadelphia positive (Ph-pos) chronic myeloid leukemia (CML).[1,2] However, about 5% of the patients must discontinue imatinib due to adverse events (AEs) and about 20% of the patients fail to respond adequately, according to the European LeukemiaNet criteria.[3] In CML patients resistant or intolerant to imatinib, alternative treatments are needed. Nilotinib (Tasigna®, formerly AMN107; Novartis Pharmaceuticals, NJ) is an oral aminophenylpyrimidine derivative that has been rationally designed to be more selective against the Bcr-Abl tyrosine kinase than imatinib. The higher selectivity results in a superior potency against imatinib-resistant cell lines, including most of the cell lines which bear mutations, and also in a lower incidence of adverse events.[4,5] Nilotinib has proved to be effective and safe in large studies involving patients with imatinib-resistant and/or intolerant CML; however, a significant (up to 18%) incidence of grade 3-4 pancreatic enzyme elevation has been reported.[6-8] Enzyme increase was not associated to acute pancreatitis in the great majority of cases; nonetheless, no data have yet been reported which describe the behavior of pancreatic enzymes over time and the clinical relevance of these laboratory alterations. For this purpose, we report our experience with 37 imatinib-resistant or intolerant CML patients who were treated with 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 NCT00302016). The studies were conducted in accordance with the Declaration of Helsinki. Both studies were approved by the ethics committee of the St. Orsola-Malpighi University Hospital and all patients gave written informed consent

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according to institutional guidelines. Enrolment criteria have been described elsewhere.[6] 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 biochemistries were obtained weekly for the first eight weeks, and thereafter every two 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.[3] Safety assessments included: evaluation of adverse events, hematologic and biochemical testing, urinanalysis, 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 3.0.

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), hematologic toxicity (2). Median follow-up of living patients was 29 months (range, 9-42).

Incidence and severity of pancreatic enzyme elevations

Lipase and amylase serum levels have been performed in all patients every 1-3 months, according to protocol requirements and to medical indications, during the entire course of nilotinib therapy. Fasting serum 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 1). 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 three 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 2 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

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

Pt (sex)	Age (yrs) at nilotinib start	Disease status	Previous therapies	Causes of IM discontinuation	Lipase increase grade 2 N. of episodes	Lipase increase grade 2 Total duration (days)	Lipase increase grade 3 N. of episodes	Lipase increase grade 3 Total duration (days)	Amylase increase grade 2 N. of episodes	Amylase increase grade 2 Total duration (days)	Enzyme elevation at last follow-up	Therapy at last contact*	Status at last follow-up	Follow-up (mos)
SA (M)	51	CP	IM	resistance	1[a]	93	0	NA	0	NA	no	Nilo 400 mg BID[1]	alive CCgR	39
GV (M)	68	AP	IM	resistance	1	90	0	NA	0	NA	no	Nilo 400 mg BID	alive CCgR	33
AS (M)	47	CP	IFN, IM, alloHSCT	adverse event (skin)	0	NA	2[b]	52	0	NA	no	Nilo 400 mg BID[2]	alive CCgR	19
AP (F)	43	CP	IM	adverse event (neutropenia)	0	NA	1[c]	15	0	NA	no	Nilo 400 mg BID[3]	alive CCgR	36
PG (F)	36	CP	IM, dasatinib	resistance	0	NA	1	12	0	NA	no	Nilo 400 mg OAD	alive minorCgR	17
PD (M)	54	CP	IM	resistance	0	NA	0	NA	1[d]	180	yes (amylase) grade 1	Nilo 400 mg OAD[4]	alive CCgR	18
MG (M)	58	CP	IFN, IM	resistance	1	19	1	7	1	27	no	Nilo 400 mg OAD	alive CCgR	14
MB (M)	51	CP	IFN, IM, ASCT	resistance	1	15	6[^]	510	5	120	yes (lipase) grade 3	Nilo 400 mg OAD[5]	alive CCgR	42

*[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. *Concomitant drugs: 1) alfuzosin, allopurinol, atenolol; 2) acetylsalicylic acid, metoprolol; 3) furosemid, lorazepam.; 4) omeprazole; 5) alfuzosin, allopurinol. [^]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.*

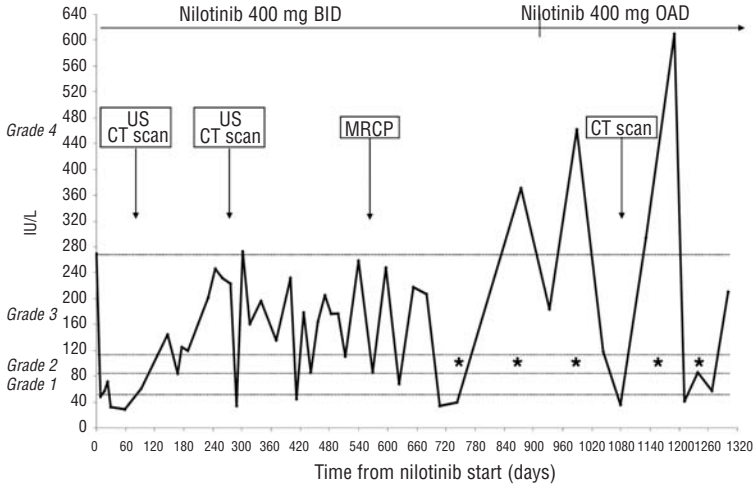

Figure 1. Lipase levels during nilotinib treatment of patient MB. Stars represent the time points when concomitant grade 2 amylase level elevations were recorded. US: ultrasonography; CT: computed tomography; MRCP: magnetic resonance colangiopancreatography.

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 enzyme 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 hyperenzymemia. During treatment, all patients had maintained the same lifestyle and alimentary habits; in particular, alcohol abuse was excluded in all cases. Concomitant drugs were also recorded (Table 1), but none of them seemed to be related to pancreatic hyperenzymemia.

Clinical implications of pancreatic enzyme 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, bile 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 behavior; the phenomenon was monitored with 15-day clinical and laboratory tests, and was investigated with 3 computed tomography scans and one MRCP (magnetic resonance colangio-pancreatography), all of which failed to reveal abdominal anatomic alterations. Endoscopic retrograde pancreatography[9] and exocrine pancreatic function study by the secretin-cerulein test[10] 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 4 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 interruption was similar in CP-CML patients with or without pancreatic enzyme elevations (19 days, range 0-50, *vs.* one day, range 0-146, respectively, p=0.23). 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 cytogenetic response (versus 9 complete responders out of 17 chronic phase patients without enzyme elevation, p=0.19).

Discussion and Results

Pancreatic enzyme 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 eight months.[6,8]

The reason for pancreatic enzyme 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 signaling proteins, nucleo-cytoplasmic shuttling, DNA and actin binding sites, thus integrating information from multiple pathways in different cellular compartments.[11]

Therefore, it is possible that c-Abl inhibition might interfere with the molecular mechanisms regulating pancreatic cell death, inducing pancreatic damage. Another possibility is that the drug may act on unknown intracellular pathways involved in calcium release from the intracellular acinar stores, which regulate exocrine pancreatic secretion,[12,13] or may promote the accumulation of fatty acid inside the pancreatic acinar cell, which disturbs exocytosis.[14] However, pancreatic enzyme elevations are rarely observed during exposure to other ABL kinase inhibitors, and the molecular mechanisms of action of nilotinib on pancreatic enzyme level deserves to be investigated. 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 enzyme is usually an expression of pancreatic disease;[15] 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 enzyme elevations persisting over time with considerable fluctuations, in the absence of pancreatic disease, a 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 two 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 precautionarily reduced in 2 cases only. More importantly, no patient developed acute pancreatitis or clinical signs of pancreatic disease, such as pancreatic-type pain, obstructive jaundice, maldigestion, diabetes, pancreatic cysts and ascites.

Authorship and Disclosures

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

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