Alterations in creatine kinase, phosphate and lipid values in patients with chronic myeloid leukemia during treatment with imatinib

Imatinib, the treatment of choice for chronic myeloid leukemia, is generally well tolerated. We present here data from a retrospective analysis on metabolic abnormalities occurring during therapy which show increased creatine kinase, inverse creatine kinase-phosphate correlation, cholesterol and triglyceride values.

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Common side effects of imatinib are edema, muscle cramps, diarrhea, osteoarticular pain, hair hypopigmentation, skin rashes and conjunctival inflammation.[1] Rarer toxicities include gynecomastia,[2] liver damage,[3] cytopenia.

From November 1999 to October 2004, 50 patients with CML (45 chronic phase [CP], 5 accelerated phase [AP]), were treated with imatinib at San Gerardo Hospital (University of Milan Bicocca, Monza, Italy) and at the Jewish General Hospital (McGill University, Montreal, Canada).

Patient selection was based on the development of a durable (>2 years) complete cytogenetic remission (CCyR). Patients were followed for a minimum of 24 months.

Mean CK values showed a significant increase over time (Table 1). At baseline, 1/50 (2%) patients showed abnormally high CK values; this percentage increased to 30% at 6 months (p<0.0001), 40% at 12 months (p<0.0001), 56% at 24 months (p<0.0001), 48.3% at 36 months (p<0.0001). To our knowledge, this represents the first report on an increase in CK values after imatinib treatment.

In a few cases (4%), treatment was interrupted as a precaution because of high (>1000) CK. No clinical signs of myopathy were noted and CK values returned within the normal range after imatinib discontinuation. Once imatinib was restarted, CK values tended to rise again.

Myocardial-CK (CK-MB) values were evaluated in 6 patients with a large increase in total CK levels (>800) and found to be normal. Therefore, the source of elevated CK in these patients did not derive from myocardium. We assessed the correlation between CK increase and imatinib dosage. Patients treated with more than 400 mg of imatinib/day had higher values than those treated with 400 mg/day (p=0.0253, Table 2).

Several patients reported the onset of muscle cramps during treatment. However no correlation between high CK and cramps was present (p=0.7501, *data not shown*).

A significant decrease in PO was present at 6 and 12 months (Table 1). A decrease in phosphate during treatment with imatinib has been reported.[4] However, no correlation between PO and CK was performed. We analyzed the possible correlation between phosphate and CK values. We selected 30 patients showing increased CK at any time during imatinib treatment. The mean CK values of these patients at baseline, 6, 12, 24 and 36 months were plotted against the mean PO values of the same patients. A significant (p=0.0239) inverse correlation between PO and CK values was observed, suggesting a possible link between these two abnormalities (*data not shown*).

A progressive decrease in C and TG was also observed during treatment (Table 1). Three patients with high C/TG levels obtained a satisfactory stabilization of values after starting imatinib. In these patients a pharmacological treatment previously used to control the hyperlipidemia was no longer needed.

The pathogenesis of these side effects is unknown. C-kit is inhibited by imatinib. This tyrosine kinase is a transmembrane glycoprotein and its signaling is critical for normal development and survival of hematopoietic progenitor cells, mast cells, melanocytes, germ cells and interstitial cells of Cajal (intestinal pacemaker cells). The inhibition of c-kit in Cajal cells could play a role in the occurrence of diarrhea in imatinib treated patients. An obvious consequence of diarrhea is malabsorption which could cause a decrease in serum calcium levels,[5] resulting in a secondary hyperparathyroidism which causes increased excretion of the phosphorus and subsequent decrease in phosphate. The latter can cause muscular distress that, if prolonged, can lead to increased CK levels.[6]

The mechanism of C/TG decrease is not clear. In addition to a possible reduction in absorption, a possible role could be attributed to the PDGF receptor inhibition by imatinib,[7] with a resulting decrease in lipoprotein lipase (LPL) synthesis and, therefore, in intermediate-density lipoproteins (IDL) with a consequent

Table 1. Fifty patients were analyzed; median age was 53 years (range 26-75 years), thirty-five patients were male and fifteen females. The table presents mean values of CK, PO, TG and C at different time points; the values in parentheses represent 95% confidence intervals (95%CI). All statistical analyses are performed in comparison with baseline values. Statistical analysis was performed using Student's t-tests, Fisher's test and χ^2 test. All the statistical analyses were performed using Graph Pad Prism 4 (Graph Pad Software, Inc.).

	Normal range	*Baseline*	*6 months*	*12 months*	*24 months*	*36 months*
CK	20-180 U/L	64 U/L (52-76)	191 U/L (125-257) p<0.0002	188 U/L (149-227) p<0.0001	200 U/L (152-248) p<0.001	199 U/L (157-241) p<0.0001
PO	2-5 mg/dL	2.8 mg/dL (2.5-3.1	2.3 mg/dL (2-2.6) p=0.01	2.3 mg/dL (2-2.5) p=0.01	2.4 mg/dL (2.2-2.6) p=0.06	2.5 mg/dL (2.2-2.8) p=0.2
TG	50-200 mg/dL	220 mg/dL (119-322)	116 mg/dL (87-145) p=0.01	103 mg/dL (82-124) p=0.01	131 mg/dL (108-163) p=0.05	Not done
C	130-200 mg/dL	170 mg/dL (155-185)	150 mg/dL (141-159) p=0.0006	151 mg/dL (140-162) p=0.0006	158 mg/dL (147-169) p=0.6	Not done

Table 2. Correlation between the increase in creatine Kinase values and imatinib dose (400 mg versus higher dosages) in patients that reached 36 months of follow-up (29 patients).

Imatinib dose	*CK increase*	*CK normal*	*Total*
400 mg	5	12	17
> 400 mg	9	3	12
Total	14	15	29
	p=0.0253		

decrease in LDL and C synthesis.[7]

In conclusion, CK increase is a common finding in patients treated with imatinib. These data are not cause for concern. No signs of myopathy were observed during the period of follow-up. Neither were increasd CK-MB values seen, supporting data on the cardiac safety of imatinib.[8-10]

The finding that C/TG values decreased over time could also be of interest to patients with dislipidemias.

Our data could help define abnormalities related to imatinib therapy for easier clinical recognition.

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