

## Changes in Blood Concentration of Imatinib and Creatine Kinase in A Chronic Myeloid Leukemia Patient With Peritoneal Dialysis



### Medical Science

KEYWORDS :

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The IRIS trial results (International Randomized Study of Interferon and STI571) showed that imatinib is more effective than interferon with a low dose of cytarabine [1]. Based on these results, imatinib is now used as a first line therapy for Philadelphia chromosome positive chronic myeloid leukemia (CML). Imatinib therapy is a lifelong approach that requires daily medication and frequent monitoring. Its common side effects include edema, muscle cramps, diarrhea, skin rash, osteoarticular pain, and hair hypopigmentation [2]. Myalgias and muscle complication are common problems in CML patients who are treated with imatinib [3]. However, the elevation of creatine kinase (CK) has only been reported in 0.1-1% of patients. Changes of the blood concentration of imatinib and CK remain unreported in patients with peritoneal dialysis (PD). Here we report the changes in the blood concentration of imatinib and CK in chronic myeloid leukemia patients with peritoneal dialysis.

A 37-year-old chronic glomerulonephritis male was referred to our hospital on April 2010 with an elevated white blood cell count. His white blood cell count was 349X10<sup>9</sup>/L, his red blood cell count was 402X10<sup>10</sup>/L, and his platelet cell count was 450X10<sup>9</sup>/L. The polymerase chain reaction of BCR-ABL were resulted positive in his bone marrow cells. He was diagnosed with chronic-phase CML. He was started on 200 mg of imatinib. The dose was gradually escalated but his treatment was changed to hydroxyurea because his kidney function worsened. Complete hematological response was not obtained by the hydroxyurea treatment. In April 2013, he was hospitalized in our institution at the start of PD because his kidney function had worsened. He was started on 200mg of imatinib, and we gradually increased the dose while paying close attention to potential side effects. The hydroxyurea was eventually stopped. The patient's imatinib concentration was obtained before its morning intake (trough level) and monitored during the imatinib treatment. The imatinib concentration gradually elevated based on the dosage increase. Although his white blood cell count decreased to 13x10<sup>4</sup>m<sup>3</sup>, his platelets elevated to 710x10<sup>4</sup>m<sup>3</sup>. After a three-week administration of 800mg of imatinib, he suddenly experienced weakness, muscle pain, and a rise of CK to 5117 U/L. His blood concentration of imatinib elevated to 2639 ng/ml. He did not drink alcohol. His electrolytes and endocrine levels were normal. At the time of the CK elevation, the concomitant medications were 20mg of furosemide, 10mg of febuxostat, 8mg of azelnidipine, and 300 mg of ursodeoxycholic acid. CK levels were decreased immediately after imatinib was discontinued (Fig. 1a).

In July 2013, he was administered 200mg of imatinib due to the progression of CML. We gradually increased the imatinib dose and monitored his blood concentration and CK levels. After a six-week administration of 600mg of imatinib, his CK (954 U/L) elevated again without any symptoms, and his blood concentration of imatinib rose to 1251 ng/ml. The concomitant medication was 300 mg of ursodeoxycholic acid during the CK elevation. CK improved, and the blood concentration of imatinib decreased to 387 ng/ml after its reduction (300mg, Fig. 1b). Although the elevation of blood concentration, imatinib was not detected in waste fluid of PD (below 50 ng/ml). Although complete hematological remission (CHR) was obtained, he still failed to attain complete molecular remission (CMR) after more than one year of imatinib administration.

Imatinib is mainly metabolized in the liver and eliminated in the biliary route [4]. Successful imatinib treatment was previously reported in CML or gastrointestinal stromal tumors with hemodialysis patients [5-7]. These reports showed that imatinib's maximum concentration was 3340ng/ml, its trough level was 1540ng/ml, and its half-life was 18.2 hours in patients who received 400mg. These changes of imatinib had almost the same metabolism as in patients who were administered the drug in normal renal function [5]. CK elevation was not complicated in these reports.

In our patient's case, the imatinib concentrations of the trough levels were 85 to 2639 ng/ml, which did not exceed previous reports in hemodialysis CML patients who were treated with imatinib. Although imatinib's concentration was not high, CK elevation developed. PD is the process of discharging waste by the peritoneum and approximates the kidney's operation from hemodialysis. But imatinib was not discharged by PD, so increase the burden on the liver due to congestive by the insufficient water removal or drug that resulted to consider prolongation or high peak of imatinib blood concentration unexpectedly. Unexpected side effects were considered during the imatinib administration before PD can be enforced stable.

Renal failure recovery is associated with a change of tyrosine kinase inhibitor from imatinib and dasatinib to nilotinib [8]. Some beneficial effects were also observed in a rat model [9]. Nilotinib may be more suitable to treat CML in such cases.

CK elevation is an important complication of CML patients with imatinib treatment for peritoneal dialysis. CK must be closely monitored to prevent the development of muscle injury. Nilotinib may be suitable for CML treatment with renal failure, especially when peritoneal dialysis is administered.

#### Figure legends

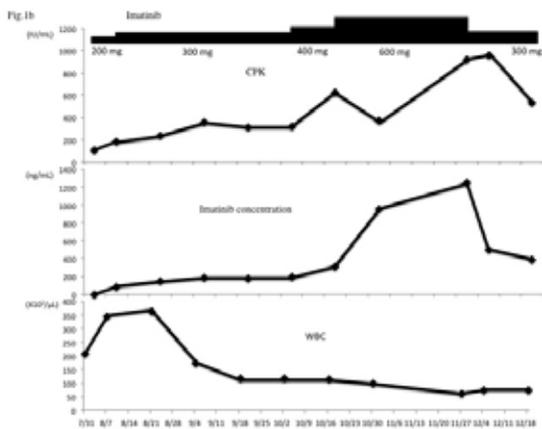
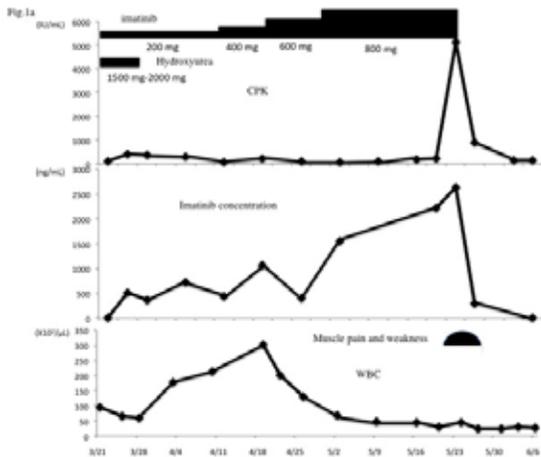
Fig. 1 Clinical course of imatinib treatment: a) Imatinib blood concentration gradually elevated based on dosage escalation. CK suddenly rose when the imatinib concentration was maximal. b) Imatinib blood concentration elevated based on imatinib dosage. CK showed an increase in CK with rise of imatinib.

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