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ORIGINAL ARTICLE

Therapeutic drug monitoring for imatinib: Current status and Indian experience

Brijesh Arora, Vikram Gota[1], Hari Menon, Manju Sengar, Reena Nair, Pankaj Patial[1], S. D. Banavali

Departments of Medical Oncology and [1]Clinical Pharmacology, Tata Memorial Centre, Mumbai, Maharashtra, India

Address for correspondence:
Dr. Brijesh Arora,
Department of Medical Oncology,
Tata Memorial Hospital, Mumbai,
Maharashtra, India.
E-mail: brijesh.aurora@gmail.com

ABSTRACT

Imatinib is the current gold standard for treatment of chronic myeloid leukemia (CML). Recent pharmacokinetic studies have shown considerable variability in trough concentrations of imatinib due to variations in its metabolism, poor compliance, or drug-drug interactions and highlighted its impact on clinical response. A trough level close to 1000 ng/mL, appears to be correlated with better cytogenetic and molecular responses. Therapeutic Drug Monitoring (TDM) for imatinib may provide useful added information on efficacy, safety and compliance than clinical assessment alone and help in clinical decision making. It may be particularly helpful in patients with suboptimal response to treatment or treatment failure, severe or rare adverse events, possible drug interactions, or suspected nonadherence. Further prospective studies are needed to confirm relationship between imatinib plasma concentrations with response, and to define effective plasma concentrations in different patient populations.

Key words: *Blood-level testing, chronic myeloid leukemia, imatinib, pharmacodynamics, pharmacokinetics, tyrosine kinase inhibitors*

INTRODUCTION

The greatest advancement in the therapy of chronic myeloid leukemia (CML) has been the introduction of imatinib mesylate (IM), a 2-phenylaminopyrimidine and selective inhibitor of BCR-ABL.[1] Imatinib produces durable responses, prolongs event-free and progression-free survival in patients with CML and is the current standard of care for this disease.[2,3] However, despite the high initial response rates, approximately 10-15% of early chronic phase patients will display primary or acquired cytogenetic resistance and even treatment failure to IM.[2,3] The key factors behind this are either biological factors such as BCR-ABL mutations or other genetic variations[4,5] and clinical features, such as the disease status or the high Sokal risk score.[1-3] More recently, it has been suggested that variations in plasma trough IM levels or other pharmacokinetic (PK)-related factors could also affect cytogenetic and molecular responses in CML.[6-8] This review attempts to present a brief summary of factors that affect imatinib PK and plasma levels, the plasma PK-response correlation and the current use of imatinib blood-level testing in various patient groups.

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WHAT IS THE CURRENT IMPACT OF IMATINIB PLASMA LEVELS ON CLINICAL OUTCOMES?

Many studies have shown a correlation between imatinib trough plasma concentration and clinical response in various tumors.[6-11] In CML, four seminal studies have examined the relationship between trough plasma imatinib concentration and cytogenetic and molecular responses so far and have shown that mean trough plasma imatinib levels were significantly higher in patients with a complete cytogenetic response (CCR) or major molecular response (MMR) at the time of assessment than in those without at the same mean daily imatinib dose between the two groups.[6-9] One of these studies also showed that cumulative estimated CCR and MMR rates differed among the quartiles of imatinib trough levels ($P = .01$ for CCyR, $P = .02$ for MMR) and on multivariate analysis, imatinib trough concentration was found to be an independent predictor of the likelihood of CCR independently of Sokal risk group. There was a trend toward better event-free survival at 5 years in patients with higher trough imatinib concentrations. It was concluded that patients were more likely to achieve a satisfactory response to therapy if an adequate imatinib trough plasma concentration was achieved and maintained.[6] Most recently, the 1-year data from the phase III tyrosine kinase dose optimization

study also confirm a correlation between IM trough plasma concentrations and clinical response.[8] Conversely, a recent small study of 78 CML patients failed to find any correlation between IM plasma concentration and response.[10] However, this study was limited by potential bias in the patient population, small patient numbers and heterogeneous sampling times.[10,11]

Correlation of imatinib plasma concentration with toxicity has not been consistently observed. In one study, a statistically significant correlation was observed between free drug exposure and toxicity in CML.[12] However, in the IRIS study, no correlation was observed except that higher imatinib concentrations were associated with greater risk of fluid retention, rash, myalgia or anemia, but less risk of fatigue, abdominal pain, joint pain or neutropenia. The authors suggested that the risk of some adverse effects may be influenced by disease burden or the speed of response to therapy. Discontinuations because of adverse events did not vary significantly among the quartiles.[6] Thus, the role of imatinib plasma concentrations in predicting toxicity remains to be confirmed.

HOW VARIABLE IS IMATINIB PLASMA EXPOSURE?

IM has a good PK profile with rapid oral absorption uninfluenced by food, almost-complete bioavailability, a proportionate dose-response relationship and a terminal elimination half-life (~18 h) compatible with once-daily dosing.[13,14] Steady-state plasma concentration is achieved after 5-7 days of therapy.[13] Although, intrapatient variability in imatinib trough blood concentrations is small, but the interpatient variability in exposure to imatinib at the same dose can be substantial with a coefficient of variation of 40-60%.[6,7,13] Data from the phase III IRIS study reported by Larson *et al.* also showed high interpatient variability in plasma imatinib concentrations. Trough plasma imatinib was measured at steady state before morning dosing on day 29 in 351 patients receiving 400 mg/day. The overall mean Cmin was 979 ± 530 ng/ml, with a coefficient of variation of 54.1%. CGP74588, the active N-desmethyl metabolite of imatinib, had a similar coefficient of variation for trough concentrations (43.6%).[6] Large interpatient variability of IM trough levels concentrations ranging from 181 to 2947 ng/ml was also noted in a French study in patients with CML receiving IM at 400 or 600 mg/day.[7]

WHAT ARE THE POTENTIAL REASONS FOR VARIATIONS IN IMATINIB PLASMA CONCENTRATIONS?

There are many potential reasons; first is poor compliance due need for prolonged life-long therapy. In general, 95% adherence is generally considered the goal for patients with life-threatening diseases.[15] In a recent analysis, only 41% of patients had good compliance, which continued to decrease with time.[15] Secondly, many demographic factors including sex, age, body weight and BSA, have been shown to have mild impact on imatinib exposure.[6,16] Third, imatinib is metabolized by the cytochrome P450 (Cyp), mainly through its CYP3A4 isoform.[17] Interpatient or interracial variability in CYP3A4 activity may lead to variable imatinib exposure among patients.[18] Furthermore, CYP3A4 activity can be affected by drug-drug interactions due to simultaneous use of other drugs, which are either cytochrome enzyme inhibitors or inducers.[16] Finally, imatinib levels may be altered by the gastrointestinal tract diseases or anatomic abnormalities due to poor absorption and differences in plasma protein binding of IM.[19,20]

HOW TO MEASURE TROUGH PLASMA CONCENTRATIONS?

Imatinib exposure may be monitored by measuring the area under the curve of plasma concentration versus time and peak concentrations or trough concentration estimation. Of these, trough plasma concentrations of imatinib are easily estimable and are most widely assayed. Trough concentration blood samples are collected before morning dosing at steady state and are typically determined using rapid, simple, sensitive and specific liquid chromatography–mass spectrometry (LC-MS) or high-performance liquid chromatography (HPLC) coupled with tandem mass spectrometry protocols which have been validated very well.[6,7,21,22] Alternatively, HPLC coupled with ultraviolet (UV) diode array detection can also be used to quantify imatinib. However, this method needs to be further validated as per the current Food and Drug Administration guidelines. Novel tools such as measurement of intracellular imatinib concentrations or activity of cellular uptake/efflux transporters such as multidrug resistance protein 1 (also known as P-glycoprotein), multixenobiotic resistance protein (also known as breast-cancer resistance protein) and human organic cation transporter 1 are being used primarily for research purposes and these tests are not widely available.[23-26]

WHAT IS THE THERAPEUTIC CONCENTRATION WINDOW FOR IMATINIB?

This has not been clearly defined. In the two seminal studies, plasma imatinib concentrations of more than 1002 ng/ml and more than 1009 ng/ml were significantly associated with the achievement of good cytogenetic and molecular responses. Hence, it is suggested that ensuring plasma trough concentrations at or above the mean population concentration of 1000 ng/ml could be critical for achieving superior rates of CCR and MMR.[6,7]

However, it would be imperative to study the clinical impact of maintaining imatinib concentrations over a sustained period since the importance of factors such as intrapatient variability over time, interactions with other medications and the effect of dose changes and treatment interruptions has not been fully investigated.

WHEN TO MEASURE THE LEVELS?

Therapeutic drug monitoring (TDM) could be of value in many clinical situations: First, when patients have a suboptimal response or treatment failure, measurement of trough plasma imatinib concentration could further assist the clinician in deciding whether to escalate the dose in addition to other important factors influencing decision making.[27] Second, when patients develop unusually severe adverse reactions and have supratherapeutic levels, a dose reduction may help as shown in recent small reports.[28] Third, when the clinician suspects a drug-drug interaction because of concomitant use of a cytochrome inducer or inhibitor or drug with unknown interaction with imatinib and measurement shows low imatinib concentration, imatinib dose should be increased or suspect drug stopped and replaced with a safer drug. A repeat level after the intervention should be done to ensure the "therapeutic" concentration of imatinib. Finally, in case of a poor level prompted by suboptimal response, drug compliance should be checked. Compliance monitoring can be done through random unscheduled measurement of trough plasma concentration. Although, measurement of plasma concentrations may assist in these difficult cases, decisions regarding the need for treatment interruption, dose reduction or change of therapy should always be based on the overall clinical situation until further data is available.

WHAT ARE THE PITFALLS OF MEASURING THE LEVELS?

Measuring trough plasma concentrations provides an additional tool for the management of patients taking imatinib especially if a patient fails to achieve a satisfactory response in accordance with published recommendations or has severe or unusual toxicity. Since there is no data on the impact of changes in therapeutic strategy based on trough plasma concentrations, it cannot be considered a standard therapeutic tool. As there are multiple factors in addition to plasma exposure that affect response, the therapeutic threshold of 1000 ng/ml is currently accepted as a population mean value associated with clinical response and not the target concentration for a specific patient. Furthermore, there is still limited data on the value of longitudinal measurement of trough plasma concentrations, the concentrations attained in patients receiving higher doses (>400 mg) or twice daily schedule and changes in plasma concentrations after alterations in dose. A prospective clinical trial examining the impact of dose increases in patients with low plasma levels, is in progress (monitoring imatinib) and would, hopefully, be able to address these issues.[29] Thus, whenever measured, plasma concentrations should be interpreted and decisions made in the context of all the clinical information available.

WHAT ARE THE IMATINIB LEVELS IN INDIAN POPULATION?

Development of a novel HPLC based method

The success of TDM lies in establishing an accurate, simple, rapid and cheap method for assay. Till recently, the only assay method available for imatinib was based on LC-MS.[21,22] This technique is quite cumbersome, expensive and cannot be used for routine TDM. We developed a rapid and sensitive HPLC method with UV detection for the estimation of imatinib from the plasma of patients with CML. The robustness of the method was checked by performing first dose PK on blood samples from four patients who had been administered IM (100 mg) in an oral dose. Samples were prepared in a simple and single step by precipitating the plasma proteins with methanol and 50 μl aliquot from supernatant was subjected for analysis. Assay was conducted using a C8 column under isocratic elution with 0.02M potassium dihydrogen phosphate-acetonitrile (7:3, v/v) at a flow rate of 1 ml/min and detected using photodiode array at 265 nm. Calibration plots in spiked plasma were linear in a concentration range of 0.05-25 μg/ml. The inter- and intra-day variation of the standard curve was <4% (relative standard deviation). This method has proved be a simple and quick method for the estimation of imatinib from the plasma.

Analysis of imatinib trough levels

Indian population differs from the Caucasian race with regard to CYP3A4 activity. Therefore, we sought to determine the PK of imatinib in Indian patients and compare it with published literature from west. As an off shoot, the role of TDM in predicting response and toxicity to imatinib is also being evaluated. In newly diagnosed CML-chronic phase cases, a single blood sample is being collected on day 8 and day 29 prior to dosing, for the estimation of IM trough concentration at steady state using HPLC. Bone marrow and peripheral blood examination are being done to assess response as per the standard guidelines. Information on adverse events is being collected throughout the duration of the study. CYP3A4 genotyping is being done in all patients by polymerase chain reaction-restriction fragment length polymorphism method.

Imatinib exposure in Indian population

Preliminary analysis of above mentioned study was recently conducted. Trough plasma imatinib levels were measured at steady state before morning dosing on day 8 and 29 in 46 patients receiving 400 mg/day. The overall mean Cmin on day-8 was 1974 ± 1348 ng/ml and on day 29 was 2107 ± 1211 ng/ml, with a coefficient of variation of 68.3% on day 8 and 57.5% on day 29. These levels are clearly better than the published results from French and IRIS studies conducted in Caucasian population, which showed a mean Cmin of 1058 ± 557 ng/ml and 979 ± 530 ng/ml respectively.[6,7] This shows that Indian patients may achieve better imatinib plasma concentrations compared with western population. This also confirms that day 29 steady state levels are superior than day 8 levels since 22% patients had subtherapeutic levels (<1000 ng/ml) on day 8 while only 9% were subtherapeutic by day 29. In our study, approximately 20% (3/15) on therapy patients had subtherapeutic levels; this was again significantly lower than 40-50% incidence of subtherapeutic levels in the western population.

Impact of imatinib plasma exposure on response

We compared the mean plasma levels of imatinib in good-responders (who had least major cytogenetics response at 6-12 months) with non-responders. The mean plasma level in patients achieving good response was higher compared with poor responders, although not statistically significant (2157 ± 1287 ng/ml vs. 1884 ± 809 ng/ml, respectively; $P > 0.05$). A similar small study was conducted to study the correlation of plasma levels of imatinib with the response to the therapy using the HPLC method at AIIMS, New Delhi. A total of 40 chronic myeloid leukemia patients in the chronic phase of the disease were recruited and placed into two groups of 20 patients: Imatinib responders and imatinib non-responders, respectively. Each blood sample was taken 24 h after and immediately prior to taking a 400 mg oral dose of imatinib. The mean plasma imatinib levels in the imatinib non-responders were significantly lower than those in the imatinib responders (0.70 vs. 2.34 μM/L, respectively; $P = 0.002$).[30]

CONCLUSIONS

Plasma levels of imatinib vary significantly among patients due to variable compliance, CYP enzyme polymorphism, demographic factors and drug interactions.[6,15-20] The therapeutic plasma trough imatinib concentration in CML has been considered to be 1000 ng/ml or above.[6,7] Measurement of plasma levels may be useful in patients with suboptimal response, suspected drug interaction, unusual or severe toxicity and suspect non-compliance. However, clinical parameters should guide medical management of most patients since there is variability in the test and it has not been prospectively validated. There is a need to study the role of doing minimal trough imatinib concentrations sequentially, impact of dose modification based on trough levels and impact of demographic or clinical factors such as advanced disease, higher Sokal risk scores and BCR-ABL mutations. The recently completed "The Imatinib Concentration Monitoring Evaluation study" would probably be able to answer these questions.[31] In future, TDM may become an important therapeutic tool for management of patients with CML with this added information.

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