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*Review Article*

# Therapeutic Monitoring of Imatinib Plasma Trough Levels in Chronic Myeloid Leukemia

Lokesh BN[1], Ashwathy VT[2], Vineeth VT[3], Shwetha Pondomatti[4]

[1]Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India.
[2]Department of Physiology, Jagadguru Jayadeva Murugarajendra Medical College, Davangere, Karnataka, India.
[3]Director & Head of Orthodontics, Cheddi Jaggan Dental Center, Ministry of Health, Georgetown, Guyana.
[4]Assistant professor, Department of Physiology, DD College and Research Center, Chennai, India.

Corresponding Author: Lokesh BN

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## ABSTRACT

Chronic myeloid leukemia (CML) accounts for 15% of leukemia's in adults. Imatinib belong to a class of tyrosine kinase inhibitors has bought greatest advancement in the treatment of CML. Several studies demonstrated efficacy of imatinib as first line therapy. The recommended therapeutic imatinib plasma levels should always be in a threshold range of 1000-5000 ng/ml. CML patients who achieve complete cytogenetic response (CCyR) and major molecular response (MMR) has showed higher levels of plasma imatinib. Decreased imatinib plasma trough levels over course of time results in treatment failure and disease progression. Therapeutic monitoring of imatinib plasma trough levels useful for patients those who do not achieve adequate response. The current manuscript reviews the importance of therapeutic monitoring of imatinib plasma trough levels in the management of chronic myeloid leukemia.

***Keywords:*** Chronic myeloid leukemia; Imatinib; Plasma trough levels; Complete cytogenetic response; Major molecular response.

## INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative, malignant disorder of hematopoietic stem cell. [1] CML constitutes 40 % to 82% of all leukemia cases among adults in India. [2] The discovery of the Philadelphia (Ph) chromosome in 1960 by Peter Nowell and David Hungerford was the hallmark in unravelling the pathogenesis of CML. [3,4] In the 1980s the Ph chromosome was revealed to carry a distinctive fusion gene, termed *BCR-ABL* , [5] the generation of which is now believed to be the principal cause of the chronic phase of CML.

Imatinib, tyrosine kinase inhibitor was approved for use in May 2001 for the treatment of CML patients who failed interferon and newly diagnosed CML patients in 2003 and it has drastically improved patient survival and has become the mainstay for first line CML management. [6,7] Imatinib occupies a part of the ATP binding domain of the tyrosine kinase resulting in the kinase to be stabilised in its inactive, non-ATP binding form. [8]

Imatinib is an orally administered drug and oral bioavailability of imatinib is 98%. [9] Circulating imatinib is approximately 95% bound to plasma proteins with approximately 18 hours of elimination half-life. [10] About 49 to77% of patients achieves CCyR and about 18% to 58% achieve MMR after one year of imatinib therapy. The proportion of patients who demonstrated progression free survival (PFS) ranged between 83% and 97% and overall survival (OS) ranged between 83% and 97%. [11]

Despite of treatment of CML with standard dosage of imatinib as a first line therapy, many research studies have recognized an association between imatinib plasma trough levels and treatment efficacy. Variation in imatinib plasma trough levels may be due to poor patient adherence, genetic and environmental factors leading to elimination, drug interactions, bio transformation, variation in transporter activities and absorption. Considering the importance of the therapeutic monitoring of plasma imatinib levels in the management of CML, it is essential to understand the clinical impact of pharmacokinetics of imatinib and establish correlation between imatinib plasma levels and response in CML patients. The annual rate of treatment failure with imatinib was found to be 3.3% in the first year, 7.5% in the second year, 4.8% in the third year, 1.5% in the fourth year and 0.9% in the fifth year. The corresponding annual rates of progression to AP or BP were 1.5%, 2.8%, 1.6%, 0.9% and 0.6%, respectively. [12] Resistance to imatinib is a most important cause of treatment failure in CML. [13] Patients with satisfactory response had higher level of plasma imatinib trough levels. The present study had an objective to review the therapeutic monitoring of plasma trough levels of imatinib in CML patients with CML.

## METHODOLOGY

The present study was carried out in the form of a publication review on the important aspect of therapeutic monitoring of imatinib plasma trough levels. The study was executed using electronic databanks like PubMed Central® and Medline®. The investigation was done in English using below mentioned keywords either individually or combined or both: Chronic myeloid leukemia, imatinib, plasma trough levels, pharmacokinetic, drug transporters, therapeutic drug monitoring (TDM). The inclusion criteria of literature were: Scientific content of the topic, publication details, availability and their correlation with objectives of the current study.

## DISCUSSION

### Therapeutic monitoring of imatinib plasma trough levels

Inadequate plasma concentration of imatinib may be one of causes of primary resistance. Poor patient adherence, absorption, excessive binding of imatinib to plasma protein alpha 1 acid glycoprotein may reduce the therapeutic effect of imatinib. [14,15] The trough plasma levels of imatinib were significantly higher in patients achieving CCyR and MMR at 12months. [15] Decreased intracellular concentration of imatinib due to reduced influx by OCT1 or increased efflux by Pgp has its own role in imatinib resistance, variation in metabolism mainly by cytochrome P3A4 (CYP3A4) and CYP3A5enzyme system, minorly by CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 [16,17] and the drug interactions. The mean plasma trough levels at steady state with dose rate of 400mg is 1.46 mm/l. [18] The recommended therapeutic levels of imatinib with dose rate of 400 mg should always be in a threshold range of 1-5 mm/l. [19] Druker et al [18] and Peng et al [20] observed that complete hematological response was achieved in patients when

their plasma imatinib trough levels were >1000 ng/ml and an poor hematological response at low plasma levels of imatinib. In a study conducted by Picard et al [15] disclosed that the patients with cytogenetic response showed mean plasma imatinib trough levels >1000 ng/ml. Study done by Larson et al [21] observed that higher rates of discontinuation was seen in patients with low imatinib plasma trough levels. This implies that to achieve satisfactory response there should be optimal levels of imatinib in plasma.

Patients with CML who achieve CCyR and MMR showed higher levels of imatinib plasma concentration. The clinical value of monitoring imatinib plasma levels may be useful in determining patient adherence to therapy.

Below mentioned studies data in table 1 implies the importance of monitoring the plasma imatinib trough levels to achieve satisfactory cytogenetic and molecular response in patients with CML.

**Table 1. Plasma trough levels of imatinib in published studies**

| Studies of CML and dose (mg) | Sample size | Responders Mean (ng/ml) | Non responders Mean (ng/ml) | p value |
|---|---|---|---|---|
| Larson et al (2008) [21] 400-800 mg | 351 | 1009 (±544)[b] N=297 | 812 (±409)[b] N=54 | 0.01 |
| Takahanshi et al (2010) [22] 50-800 mg | 254 | 1057 (±585)[b] N=218 | 835 (±524)[b] N=36 | 0.033 |
| Michowitz etal (2012) [23] 400-800 mg | 191 | 1078(±545)[b] N=131 | 827(±323)[b] N=16 | 0.045 |
| Picard et al (2007) [15] 400-600 mg | 68 | 1123(±617)[b] N=56 | 694 (±556)[b] N=12 | 0.03 |
| Picard et al [b] (2007) [15] 400-600 mg | 68 | 1452 (±649)[c] N=34 | 889 (±427)[c] N=34 | 0.001 |
| Singh et al (2009) [24] 400 mg (Indian study) | 40 | 2340 (±520)[a] N=20 | 690 (±150)[a] N=20 | 0.002 |

[a]Response is defined as complete hematologic response at 3 months or major cytogenetic response at 6 months
[b]Response is defined as complete cytogenetic response
[c]Response is defined as major molecular response

## CONCLUSION

CML patients with complete cytogenetic, major molecular response had higher plasma imatinib trough levels compared who do not achieve satisfactory response. [15,21-24] A higher rate of discontinuation and disease progression was observed in patients with suboptimal concentration of imatinib in their plasma. [21] Considering these facts therapeutic drug monitoring of imatinib plasma trough levels can be a useful tool to assess the response to imatinib treatment in patients with CML. It has huge impact on therapeutic decision making.

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