

Therapeutic Drug Monitoring of Imatinib in Patients of Chronic Myeloid Leukemia – Chronic Phase

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Abstract

Introduction: Tyrosine kinase inhibitor is recommended for the initial management of chronic phase chronic myeloid leukemia (CP CML) based on the more favorable balance of toxicity and long-term disease control. **Background:** Mean trough plasma Imatinib Mesylate (IM) levels are detected to be significantly higher in patients with a complete cytogenetic response or major molecular response (MMR). **Methodology:** The primary objective of the study was to correlate the IM drug levels with MMR on two different occasions at least 3 months apart and to study the variation in the plasma trough levels of IM during the treatment with standard dose for at least 12 months. **Results:** After exclusion, 30 patients of CML-CP in MMR, on standard dose over a period of 2 years were finally analyzed. The mean IM plasma levels (IPLs) of the first sample for all patients were 1722 ± 566 ng/ml (IPL-1) with a corresponding mean molecular response (MR) 0.0257 ± 0.0279 breakpoint cluster region-abelson murine leukemia (BCR-ABL) IS % (MR-1). The mean IPLs of the second sample for all patients were 1549 ± 375 ng/ml (IPL-2) with a corresponding mean MR 0.0143 ± 0.0184 BCR-ABL IS % (MR-2). Area under the receiver operating characteristic curve for IPL-1 was 0.565 and IPL-2 was 0.639. For IM level at second point of 1800 ng/ml, the specificity for predicting MMR was 81.8% and sensitivity was 31.6%. **Conclusion:** Monitoring of trough IM plasma concentrations may become the part of standard management of CML patients.

Keywords: Chronic myeloid leukemia, imatinib, major molecular response, therapeutic drug monitoring

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of the primitive hematopoietic stem cell, accounting for 15% of adult leukemias.^[1,2] The characteristic feature of this leukemia is the presence of a balanced genetic translocation between chromosomes 22 and 9, termed as Philadelphia chromosome. The resulting Breakpoint Cluster Region-Abelson Murine Leukemia (BCR-ABL) fusion oncogene is translated into the BCR-ABL oncoprotein, a constitutively active tyrosine kinase activating a number of signal transduction pathways downstream which affects the growth and survival of hematopoietic cells.^[1-3] Imatinib mesylate (IM) is a first-generation competitive inhibitor of Bcr-Abl tyrosine kinase, involved in CML pathogenesis. This drug is the current standard of care for this disease and produces durable responses, prolongs event-free survival and overall survival. Monitoring of clinical, including cytogenetic

and molecular response (MR) in CML patients is the standard management. Complete cytogenetic response (CCyR) is defined as 0% Philadelphia chromosome-positive cells in the bone marrow. Major molecular response (MMR) is defined as a 3 logarithm reduction of BCR-ABL transcripts, quantified from peripheral blood using real-time quantitative reverse-transcriptase polymerase chain reaction (RQ-PCR).^[1-3] It is also well studied that variations in the plasma trough IM levels or other pharmacokinetic (PK) factors could also affect cytogenetic and MRs in CML. Although PK studies showed that plasma trough concentrations are correlated with dose, considerable inter-individual variability has also been

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observed. PK variability may also explain variable responses to IM therapy. Various cellular mechanisms of resistance to IM are identified as gene mutations in the kinase domain of BCR-ABL, BCR-ABL gene amplification, over-expression of Src-related kinases, and drug efflux mediated by the P-glycoprotein which is encoded by the MDR-1 gene. Ineffective drug regimen can be identified by too low trough IM plasma levels (IPLs), which may be insufficient to achieve CCyR or MMR.^[1-3] Therapeutic drug monitoring (TDM) of IM levels is likely to help in the better management of CML patients. It may be particularly useful in identifying the cause leading to loss of sustained MR in CML-chronic phase (CP) patients with suboptimal response to treatment or treatment failure. It may help in identifying severe or rare adverse events (AEs), possible drug interactions, or suspected nonadherence. It may also help in establishing the safety of generic IM use and help formulate guidelines on its use in the patients suffering from CML-CP. To test this hypothesis, we measured trough IPLs by liquid chromatography mass spectrometry (LCMS) method in CML-CP patients who were in MMR, on two different occasions (at least >3 months apart) during the course of treatment with standard dose IM (400 mg once daily). IM levels and the MR were then correlated with the likelihood of sustaining MMR.

METHODOLOGY

The study was approved by ethical committee permission letter no CHAFB/17/2017 dated June 26, 2017. The present study was aimed to measure the trough plasma levels of IM in patients taking the drug for CML-CP. The primary objective of the study was to correlate the IM drug levels with MR on two different occasions at least 3 months apart and to study the variation in the plasma trough levels of IM during the treatment of CML-CP patients, treated with standard dose IM 400 mg once daily for at least 12 months.

The secondary objective of the study was to establish the therapeutic efficacy of the cheaper generic IM brands available in our set up and to establish the protocol for the measurement of trough IPLs by LCMS method, by monitoring and achieving the recommended trough plasma IM levels to maintain a sustained MMR in these patients.

A total of 50 patients of CML were enrolled in the study from Hematology outpatient department from July 1, 2017 to September 30, 2019 (27 months). All patients provided written informed consent to participate in this study. Patients were counseled and ensured for optimal drug compliance before and during the study. The study was approved by the local Institutional Ethics Committee. The drug IM was available as multiple different cheaper generic brands in our setup, and the patients received the available generic IM at different time points during the course of their treatment. The inclusion criteria for the study were: Patients diagnosed with CML-CP for at least 12 months and treated with standard-dose IM 400 mg once daily and had achieved MMR by molecular monitoring

of BCR-ABL transcript levels (by International Scale [IS] with real-time RQ-PCR [BCR-ABL (IS) by RQ-PCR]). Patients were excluded if on higher doses of IM (>400 mg per day), accelerated phase or blast crisis at diagnosis or during study period, any blood component transfusion within the past 3 months, history of co-existent other malignancy, chronic liver disease, chronic kidney disease, blood collection performed out of the trough concentration time limits, poor compliance or nonadherence to treatment (missing >3 doses of IM per month), and identification of gene mutation(s) in the kinase domain of BCR-ABL tested if patient not achieving target cytogenetic or MR time points during the treatment course of CML-CP with IM.

Three milliliters blood were collected by venipuncture for monitoring of trough plasma levels of IM in plain sterile vacutainer before the administration of morning daily dose (22–25 h after the last dose) at steady state. The blood samples were collected by venipuncture twice from each patient at an interval of 12 months (at least more than 3 months, as per protocol) at the study center. This was done on the occasion of CML day, when a medical camp was conducted at our center on September 22, 2018, and September 22, 2019, respectively. Simultaneously, the sampling of 3 ml blood in ethylenediaminetetraacetic acid vacutainer was collected for the molecular evaluation of BCR-ABL (IS) by RQ-PCR.

To assess for MRs, the tests were performed and validated at Oncquest Laboratories Limited, a National Accreditation Board for Testing and Calibration Laboratories accredited laboratory. Total RNA was extracted from peripheral blood cells, and BCR-ABL transcript levels were quantified using real-time RQ-PCR, according to recommendations recently proposed for harmonization of results. Reverse transcription real-time PCR was performed for the BCR-ABL1 fusion transcript with normalization of transcript levels to the ABL1 transcript, calculated by IS to report BCR-ABL transcript levels. Copy number of BCR-ABL1 fusion transcripts (e13a2, e14a2, e1a2, or e19a2), ABL1 control gene was calculated based on the respective calibration curves. Minimum amplification of ABL control gene was ensured to be 10,000 copies/Retention time for reporting. Percentage ratio between quantities of BCR-ABL and the ABL transcript was generated. Results were normalized to the IS scale by multiplying the IS conversion factor. IS conversion factor was established with the aid of certified reference material calibrated to the First WHO International Genetic Reference Panel for quantification of BCR-ABL1 translocation by RQ-PCR. The assay detects major, minor and micro transcripts in BCR-ABL quantitative assay. It is a four tube format wherein forward and reverse primers targeting the respective exons for the three transcripts are added along with other PCR reagents.

MMR was defined as a reduction in BCR-ABL transcript levels of at least 3 log (<0.1%) after 12 months of IM therapy, from a standardized baseline.^[1,3] The percentage reading on the IS for the present study was interpreted as follows:

<0.1% is equivalent to MMR, which is a therapeutic target in CML; or <0.0032% (log 4.5 reduction) is equivalent to deeper complete molecular response (CMR). The sensitivity of lower limit of BCR-ABL1 transcript detection in this assay was dependent on the quality of RNA and cellularity of the sample collected. It was at least 4.5 logs below the average diagnostic level.

In this study, the trough IPLs were determined using rapid, simple, sensitive, and specific LCMS (high-performance liquid chromatography [HPLC] coupled with tandem mass spectrometry) protocols which have been well validated in countries outside India. The trough IPL measurement has been performed only at three centers in India yet, however needs stringent standardization and further validation.^[4-6] At our center, we tried to validate the LCMS protocol for plasma trough IM levels measurement. The IM levels quantification was determined using LCMS protocol at Biochemistry laboratory. Chromatography solvent system used was Methanol and Formic acid of LCMS grade. The mobile phase applied was of water with 0.1% formic acid as mobile Phase A and methanol as mobile Phase B. Solvent was applied in the gradient mode with initial mobile phase flow kept at 90% of A and 10% of B and later changed to 10% of A and 90% of B in 2 min. This flow was kept for 10 min. Mobile phase flow then switched to initial flow in 10 min. Post run time was 3 min, and total run time was kept for 13 min. The flow rate was kept at 0.4 ml/min.

After the extraction of serum from the collected samples, 200 µl of serum was mixed with 800 µl of chilled methanol to precipitate the protein. The mixture was vortexed and mixed well. The supernatant was transferred to Bond Elut Captiva ND Lipid cartridges after centrifuge at 7000 rpm for 4 min at 8°C. The vacuum was applied, and the elute collected was injected into the system. Quality control samples were prepared by spiking different serum with different and proper volume of the corresponding standards solution to make final concentration of 0.5, 2, and 4 ppm. The electron spray ionization in the positive mode was used to identify the precursor ion, product ion and to standardize the different fragmentor voltage and the collision energy required for developing the MRM transitions. Accordingly, MRM transitions were developed and tabulated before developing instrument method on column, as shown in Table 1. MRM was developed using stock solution of 100 ng/ml where compound was passed through

mass spectrometer without passing it through the column under conditions [Table 1]. The total ion chromatogram was achieved as depicted in Figure 1, and finally calibration curve was made from 0.5 ppm, 1 ppm, 2 ppm, 4 ppm, and 8 ppm standards, as depicted in Figure 2. Method validation was done by using selectivity, linearity, accuracy, precision, recovery, detection limit, and quantitation limit. Specificity in our study was measured by retention time, product ion (qualitative and quantitative) and by ratio of qualitative to quantitative ion. Calibration curve was made by using 0.5 ppm, 1 ppm, 2 ppm, 4 ppm, and 8 ppm concentration of IM [Figure 3]. Coefficient of correlation was 0.99 in our study. Reproducibility was checked by making a total of six injections. Chromatogram was monitored and checked, and it was found that retention time and area under the curves were same for all the peaks. Recovery in our study was about 80%–85%. Limit of detection and limit of quantification in our study were determined using signal/noise ratio. Limit of detection was 0.2 ppm and limit of quantification was 0.5 ppm.

Statistical analysis

All the statistical analyses were carried out using the SPSS software version 27 (IBM SPSS Software Version 27 (2020) India). Descriptives were run for all the baseline characteristics. Continuous variables were expressed as “mean ± standard deviation.” Characteristics of patients in MMR and CMR were compared using “independent *t*-test” or “Chi-square test” as appropriate. Receiver operating characteristic (ROC) curve was subsequently plotted to determine the trough levels of IM which best differentiate the patients having CMR and MMR.

RESULTS

A total of 50 patients of CML-CP as per the inclusion criteria were enrolled in the study after obtaining written informed consent. Seven patients declined to continue in the

Table 1: Multiple reaction monitoring conditions in liquid chromatography mass spectrometry

Selected peptides / conditions	Values used in LCMS
Precursor ion	494.3
Product ion	393.3
Fragmentor voltage (v)	110
Collision energy (v)	22
Cell acceleration voltage (v)	5

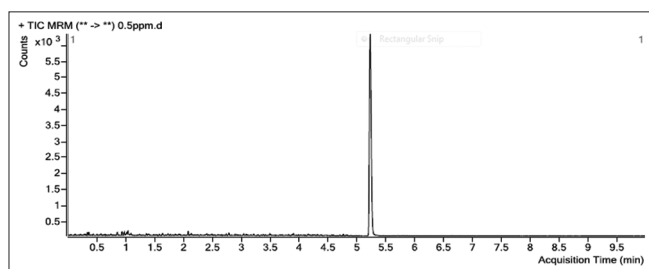


Figure 1: Sample chromatogram

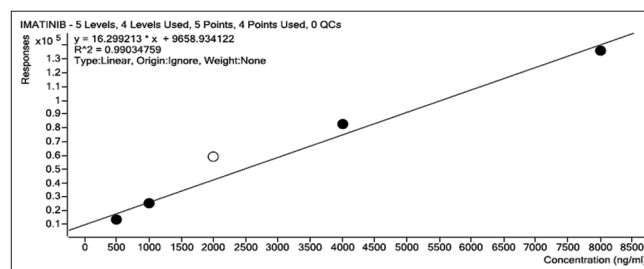


Figure 2: Calibration curve for imatinib

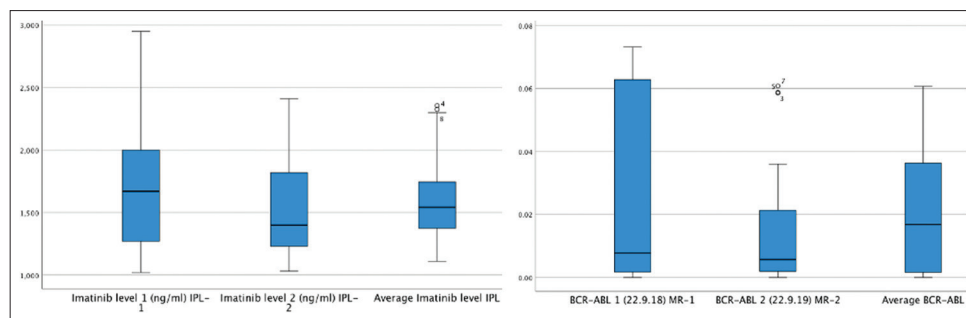


Figure 3: Box and whisker plots for IM plasma levels and molecular response

study; five patients failed first-line IM therapy and required second-generation tyrosine kinase inhibitors (2G-TKI); four patients required higher dose (>400–800 mg per day) of IM; one patient was switched to 2G-TKI due to intolerable skin reaction to IM; one patient was initiated on Treatment Free Remission; whereas two patients progressed from CP to accelerated phase during the study period. After exclusion, 30 patients of CML-CP, in MMR, on standard dose of IM (400 mg per day) being treated at this hospital over a period of 2 years who completed the study protocol were finally analyzed in the study. Baseline characteristics of CML-CP study patients on standard dose IM, in MMR are as in Table 2. Box and whisker plots [Figure 3] were drawn to show the dispersion around the mean for IPLs and MR by BCR-ABL IS % by RQ-PCR of the two samples drawn 12 months apart along with their averages. As shown in Table 2 and Figure 3, the mean IPLs of the first sample for all patients were 1722 ± 566 ng/ml (IPL-1) with a corresponding mean MR 0.0257 ± 0.0279 BCR-ABL IS % (MR-1). The mean IPLs of the second sample for all patients were 1549 ± 375 ng/ml (IPL-2) with a corresponding mean MR 0.0143 ± 0.0184 BCR-ABL IS % (MR-2). The average mean IPLs of both samples together for all patients were 1635 ± 340 ng/ml (average IPL) with a corresponding average mean MR 0.0199 ± 0.0185 BCR-ABL IS % (average MR). The trough IPLs were correlated with the MR. The IM drug levels for 1st sample analysis did not correlate with the MR (IPL-1 vs. MR-1; $r = -0.136$, $P = 0.47$). The IM drug levels for the 2nd sample analysis after a period of 12 months did not correlate with the MR (IPL-2 vs. MR-2; $r = 0.11$, $P = 0.55$). The average IM drug levels of both samples also did not have a significant correlation with the average MR (average IPL vs. average MR; $r = 0.166$, $P = 0.38$). The trough IM plasma steady state levels were then further analyzed for depth of MR between MMR and CMR, as shown in Table 3. The demographic quantitative characteristics were compared in the study patients with MMR versus CMR. As expected the difference of MR was significant, but there was no difference in the age group and IM levels in the two groups. The ROC curve was subsequently plotted for IM level at two different time point 12 months apart to determine the better determinant of MMR. Area under the curve for IPL-1 was 0.565 and IPL-2 was 0.639. For IM level at second point of 1800 ng/ml, the specificity for predicting MMR was 81.8% and sensitivity was 31.6%, as shown in Figure 4.

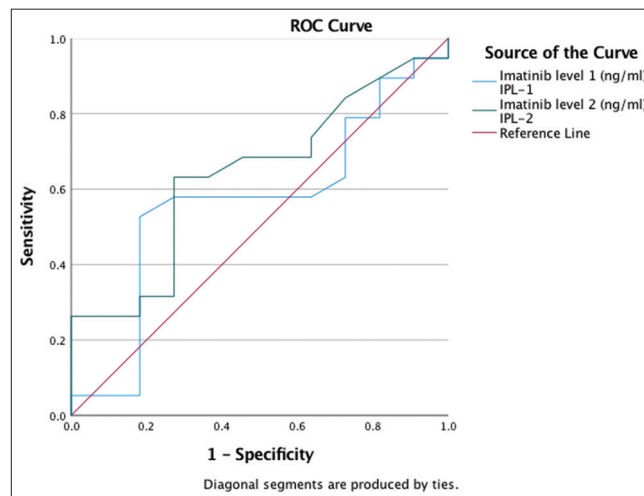


Figure 4: Receiver operating characteristic curve for imatinib (IM) levels on two occasions as a determinant for major molecular response

DISCUSSION

TDM is evolving as an important tool in the management of CML patients. By measuring IM plasma concentrations, it becomes useful to evaluate patient compliance to daily oral therapy, potential drugs interactions, treatment efficacy, and severe drug related AEs.^[7] IM level in the plasma is most widely measured by trough plasma concentration. Blood samples are collected before morning dosing at steady state and are typically determined using rapid, simple, sensitive, and specific LC-MS or HPLC coupled with tandem mass spectrometry protocols, which have been validated very well.^[1,3,8] Rezende *et al.* had developed the protocol for IM quantification, in which the total analytical run time was 4 min compared to 13 min as in our study.^[9] In this study by Rezende *et al.*, methanol and water were used, each containing 10 mM of ammonium acetate and 0.1% formic acid, whereas in the present study methanol and water containing 0.1% formic acid was used. Sample preparation in our study is also much easier. In another study by Rezende *et al.*,^[10] they have used serum as a matrix which is similar to our study as processing of the sample with serum is quick and easy. They validated the IM protocol on ultrafast liquid chromatography coupled with mass spectrometry. There are many studies where different methods to develop and validate the IM protocol by using different

Table 2: Baseline characteristics of chronic myeloid leukemia - chronic phase study patients on standard dose imatinib, in major molecular response

Characteristics	Number of patients, n (%)
Qualitative	
Gender	
Males	19 (63.3)
Females	11 (36.7)
Quantitative	
Age (years), mean±SD	53.2±13.9
MR*, mean%±SD	
MR-1	0.0257±0.0279
MR-2	0.0143±0.0184
Average MR	0.0199±0.0185
Trough IPL†, mean±SD	
IPL-1	1722±566
IPL-2	1549±375
Average IPL	1635±340

Data are mean values (mean±SD) for quantitative features. Data are proportions (%) for qualitative features, *MR indicates molecular response (in BCR-ABL transcript levels) by BCR-ABL IS% by RQ-PCR. †IPL trough imatinib plasma levels are expressed in (ng/mL). SD=Standard deviation, MR=Molecular response, IPL=Imatinib plasma levels, BCR-ABL IS=Breakpoint cluster region - abelson murine leukemia International Scale, RQ-PCR=Real-time quantitative reverse-transcriptase polymerase chain reaction

Table 3: Characteristics of chronic myeloid leukemia - chronic phase study patients, compared for major molecular response versus complete molecular response

Characteristics	MMR	CMR	Significance (P)
Qualitative, n (%)			
Gender			
Males	15 (50.0)	4 (13.3)	
Females	4 (13.3)	7 (23.4)	
Quantitative, mean±SD			
Age (years)	55.42±13.46	49.36±14.43	0.27
Trough IPL			
Average IPL	1692±293	1538±405	0.28
MR, mean%±SD			
Average MR	0.0307±0.0148	0.0013±0.0007	0.00

Data are mean values (mean±SD) for quantitative features. Data are proportions (%) for qualitative features, MR indicates molecular response (in BCR-ABL transcript levels) by BCR-ABL % (IS) by RQ-PCR, †IPL Trough imatinib plasma levels are expressed (ng/mL). SD=Standard deviation, MR=Molecular response, IPL=Imatinib plasma levels, BCR-ABL IS=Breakpoint cluster region - abelson murine leukemia International Scale, RQ-PCR=Real-time quantitative reverse-transcriptase polymerase chain reaction, MMR=Major molecular response, CMR=Complete molecular response

equipment like HPLC and HPLC coupled with tandem mass spectrometry (LCMS) have been employed. Our method is easy and less cumbersome as mobile phase composition is easy. We have used only methanol and water with formic acid. The sample preparation in our study is also very easy and can be utilized in the laboratory. Kuna *et al.* developed the protocol

by using HPLC in which the method linearity is from 10 to 60 µg/mL which is low for measurement of IM levels. In the present study, the method linearity was from 0.5 to 8 µg/mL which is well within the therapeutic range of IM.^[11]

In the present study, simple preparation steps were used for the extraction of IM from serum sample of study patients. A simple, specific, and precise method was then developed for measurement of IM trough level by LCMS protocol. We determined the minimum blood plasma concentration (“trough” level) of IM occurring just prior to taking the next dose by LCMS, as recommended for most quantitative determinations of IM in the plasma of patients with CML.^[8] However, LCMS facilities are not always available in standard hospital laboratories as the equipment is quite expensive.^[8,12]

TDM is considered as a valuable tool for monitoring drug therapy, as a close relationship exists between the plasma drug levels and clinical outcome. It is useful in dosage adjustment of drugs that exhibit marked inter-individual variability or have narrow therapeutic window. However, the role of TDM in the management of patients with CML on IM therapy is debatable.^[4,13] The present study evaluated the influence of IM trough plasma levels on MR in CML-CP patients, treated orally with standard-dose IM (400 mg once daily), and its ability to maintain a sustained MMR. The average mean trough IPLs were 1635 ± 340 ng/mL for the 30 CML-CP patients in MMR, analyzed twice over a period of 1 year, which was more than the recommended levels of >1000 ng/mL.^[1,3,4-6,14-16] Mean IM trough levels in the Indian studies are higher than those reported from other studies outside India. Arora *et al.* reported a mean trough levels of 2107 ± 1211 ng/mL in a small pivotal study involving 46 CML patients from Maharashtra.^[4] The mean trough levels reported by Malhotra *et al.* were 2070 ± 1150 ng/mL in 104 patients from Rajasthan.^[5] The mean trough levels reported by Natarajan *et al.* were 2333 ± 1112 ng/mL in 42 patients.^[6] They concluded that trough IPLs may be a marker for suboptimal response and may identify patients in whom increase of drug dose or change in therapy may be indicated. Since the Indian population is genetically diverse, such higher trough levels might also be attributed to the effect of genetic polymorphisms in genes coding for metabolizing enzymes and drug transporters, apart from differences in body surface area and body mass index.

Picard *et al.* studied the plasma trough levels of IM in 78 CML patients after at least 1 year of IM therapy. They reported that the trough levels of IM in those who attained MMR were significantly higher than those who have not attained MMR (1452 ± 649.1 vs. 869.3 ± 427.5). They also proposed a threshold imatinib level of 1002 ng/mL for optimal imatinib response. In the present study, all participants had plasma imatinib trough levels ≥1000 ng/mL, similar to the findings of Picard *et al.*^[11] We also correlated the mean IPLs with MRs in our patients determined by the BCR-ABL IS % by RQ-PCR. Out of 30 patients with MMR or deeper response, 19 were in MMR while 11 patients were in CMR. Student's *t*-test results

showed that the mean plasma IM levels in patients with MMR (1692 ± 293 ng/ml) were not significantly different from patients with deeper CMR (1538 ± 405 ng/ml) ($P = 0.28$). However, the MR measured by mean BCR-ABL IS % for the 19 patients in MMR (0.0307 ± 0.0148) was significantly different than the 11 patients with deeper CMR (0.0013 ± 0.0007) as expected by definition ($P = 0.00$). These results were in concordance with previous studies.^[17]

However, few studies have reported that no correlation exists between IM trough levels and therapeutic response.^[18,19] Forrest *et al.* studied the trough levels in 78 patients with CML after 1 year of IM therapy and reported that cytogenetic and MRs correlated with Sokal score but not with IM trough levels.^[18] Similarly, Yoshida *et al.* measured the trough levels in 38 patients after 1 year of IM therapy. They did not find any correlation between trough levels and cytogenetic and MRs. Patients with CMR had significantly higher trough levels of imatinib compared to those without CMR.^[19] However, there are some pitfalls in these studies including limited sample size and heterogeneous sampling times. Due to less number of nonresponders, these studies were not adequately powered to detect statistically significant difference in trough levels between responders and nonresponders. A summary of findings of previous studies correlating IM trough levels with MMR and comparison with the present study results are given in Table 4. There are no published data from India regarding compliance to IM, but data from the West^[17] indicate that this may be a major issue in sub-optimal responders. In our study, the measure of a patient's adherence to drug therapy was based on self-reporting by the patient and the compliance was assured by repeated counselling. Individual patient characteristics, including age, sex, race, weight and inherited differences in

drug absorption, metabolism, transport and disposition of drugs, and interactions between prescribed medications, may also affect drug levels. Sampling time error could be another source of variability, although all samples were collected within acceptable sampling time period.

In our study, patients were taking generic/biosimilar IM. The IPLs achieved in all our patients was in the therapeutic range (>1000 ng/ml), suggesting that these generic products can be considered equally effective and interchangeable in medical practice. Our study had 19 patients with MMR and 11 patients with CMR, and there was no statistically significant difference in IM levels between the two groups. Based on the results of our study and similar previous studies, it can be concluded that trough IPLs provide a good indicator of MR in IM treated CML patients.

CONCLUSION

Trough levels of IM in the therapeutic range influence the MR in CML-CP patients and emerged as independent predictor for sustaining the depth of response. Our study results emphasize that adequate plasma concentrations of IM are essential to produce optimal clinical response. IM generics are bio-equivalent and comparable in clinical efficacy and have the potential for substantial savings in CML treatment cost. Further prospective studies are needed to confirm the relationship between IM plasma concentrations with response, and to define effective plasma concentrations in the CML-CP patients in our set up.

Generic IM brands are efficacious in maintaining a sustained MMR in CML-CP patients. Monitoring of trough IM plasma concentrations may become the part of standard management of CML patients, or should at the very least be checked in the case of treatment failure or suboptimal response.

Table 4: Imatinib levels for chronic myeloid leukemia - chronic phase patients in major molecular response, comparison with previous studies with the present study

Authors (reference)	Number of patients	Imatinib levels (IPL)	Significance (P)
Picard <i>et al.</i> , 2007 ^[1]	34	1452±649	<0.001
Larson <i>et al.</i> , 2008 ^[3]	184	1006±328	
Kawaguchi <i>et al.</i> , 2009 ^[20]	16	1640±710	
Forrest <i>et al.</i> , 2009 ^[18]	51	1067±473	0.74
Takahashi <i>et al.</i> , 2010 ^[21]	166	1107±594	0.002
Ishikawa <i>et al.</i> , 2010 ^[22]	38	1092*	0.002
Awidi <i>et al.</i> , 2010 ^[12]	49	2767±781	
Marin <i>et al.</i> , 2010 ^[17]	84	900 (400-1600)	0.02
Yoshida <i>et al.</i> , 2011 ^[19]	27	1044±636	0.17
Koren-Michowitz <i>et al.</i> , 2012 ^[23]	120	976±385	
Ohnishi <i>et al.</i> , 2012 ^[24]	47	1140±436	
Gotta <i>et al.</i> , 2014 ^[25]	1286	870±326	
Malhotra <i>et al.</i> , 2014 ^[5]	104	2100±1180	0.001
Rousselot <i>et al.</i> , 2015 ^[26]	43	935±129	
Ostojic <i>et al.</i> , 2016 ^[16]	19	1574±598	
Natarajan <i>et al.</i> , 2019 ^[6]	42	2333±1112	0.001
Present study, 2020	30	1635±340	

Imatinib trough levels in the above table are expressed as mean±SD (except Ishikawa *et al.* *Which is given as median). IPL=Trough imatinib plasma levels (ng/mL)

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Conflicts of interest

There are no conflicts of interest.

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