

# The Role of Mutation Testing in Patients with Chronic Myeloid Leukemia in Chronic Phase after Imatinib Failure and Their Outcomes after Treatment Modification: Single-institutional Experience Over 13 Years

## Abstract

**Introduction:** BCR-ABL1 kinase domain mutations represent the most frequent mechanism of resistance to tyrosine kinase inhibitor (TKI) therapy, being detected in 40%–50% of imatinib-resistant patients with chronic myeloid leukemia in chronic phase (CML-CP). Over 100 BCR-ABL1 single-point mutations have been reported in patients with imatinib-resistant CML. There were few studies reported from India on BCR-ABL kinase mutations in imatinib failure patients. We present our data on imatinib resistance mutation analysis (IRMA) and use of imatinib dose hike and 2<sup>nd</sup>-generation TKI at our institute. **Materials and Methods:** All patients with a diagnosis of CML in a university hospital from June 2003 to July 2016 and who were tested for IRMA in view of imatinib failure, those in CP, and age <18 years were included in the study. **Results:** A total of 2110 cases of CML reviewed and 269 cases of CML with imatinib failure were analyzed. The male to female ratio was 1.7:1. The median age at presentation was 36 years (range: 18–66 years). Among these, 26% were primary failures and 74% were secondary failures. The treatment was modified either as imatinib dose hike or nilotinib/dasatinib. Molecular response at 12 months was achieved in 25.7% in imatinib dose hike, 46.6% in nilotinib, and 53.8% in dasatinib arms. The 4-year overall survival in mutation detected group was 37.5% and in nonmutated group was 87.7%. **Conclusion:** Imatinib-resistant mutations were more common in the cases with secondary failure though not statistically significant. T315I mutation was the common mutation found in the study. Imatinib dose hike to the failure cases resulted in optimal hematological response rates.

**Keywords:** 2<sup>nd</sup>-generation tyrosine kinase inhibitor; chronic myeloid leukemia, imatinib resistance mutation analysis

## Introduction

BCR-ABL protein, which results from a reciprocal translocation involving chromosomes 9 and 22, has a central role in the pathogenesis of chronic myeloid leukemia (CML). The BCR-ABL protein functions as a constitutively activated tyrosine kinase and the drugs are developed to specifically inhibit the BCR-ABL tyrosine kinase.<sup>[1]</sup>

BCR-ABL1 kinase domain mutations are the most frequent mechanism of resistance to tyrosine kinase inhibitor (TKI) therapy, which is detected in 40%–50% of imatinib-resistant patients with CML in chronic phase (CML-CP<sup>[2,3]</sup>). More than 100 BCR-ABL1 single-point mutations have been detected in patients with imatinib-resistant CML, which led to various levels of TKI resistance.<sup>[4]</sup> A threonine to isoleucine

substitution at the 315 residue (T315I), which forms a key H-bond interaction with TKIs, results in clinical insensitivity to imatinib, nilotinib, and dasatinib.<sup>[2,5-10]</sup> Other mutations can be inhibited to some extent by 2<sup>nd</sup>-generation TKIs (SG-TKIs).

The different mutations may therefore require different strategies to overcome resistance such as dose escalation for those that confer moderate resistance or shifting to SG-TKIs or even transplantation for more resistant mutations.<sup>[11]</sup>

## Aims and objectives

The aim of this study was to analyze BCR-ABL tyrosine kinase domain mutations in CML patients with imatinib failure and study the outcomes with imatinib dose escalation or SG-TKIs following imatinib resistance mutation analysis (IRMA).

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**Puligundla Krishna Chaitanya, Karnam Ashok Kumar, Bala Stalin, Gundeti Sadashivudu, Maddali Lakshmi Srinivas**

Department of Medical Oncology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

## Address for correspondence:

Dr. Karnam Ashok Kumar,  
Department of Medical Oncology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad - 500 082, Telangana, India.  
E-mail: ashokpillai005@gmail.com

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## Materials and Methods

All patients with a diagnosis of CML in tertiary care university hospital in South India between 2003 and July 2016 and a minimum follow-up of 12 months were included in the study. European LeukemiaNet (ELN) recommendations were used for the diagnosis and monitoring the response to treatment.<sup>[12]</sup> Sokal, Euro, and EUTOS scoring systems were used for risk stratification.<sup>[13-15]</sup> Primary failure was defined as failure to achieve a given response at a given time and secondary failure as loss of initial response to TKI at anytime.

All patients who were tested for IRMA in view of imatinib failure, those in CP, and age <18 years were included in the study and those in CML-AP and BP, age <18 years, and pregnant were excluded from the study. Direct sequencing of the BCR-ABL transcript by the Sanger method was used for IRMA testing. Overall survival (OS) was defined from the date of imatinib resistance to the date of death or last follow-up.

Fisher's exact test using Prism version 7.02, Graphpad software, LaJolla, California, USA was used to analyze the proportion of mutations depending on the type of failure. To evaluate the association between mutation status and survival, log-rank test was used. Survival probabilities were estimated by the Kaplan–Meier method and compared by the log-rank test.<sup>[16]</sup>

## Results

A total of 2110 patients of CML reviewed and 269 cases of CML with imatinib failure were analyzed. Baseline characteristics of these patients ( $n = 269$ ) were tabulated in Table 1.

The baseline hematological parameters assessed for these patients were represented in Table 2.

Molecular studies for BCR-ABL revealed the major transcript (p210 = e13a2, e14a2) in 138 cases, and in 131 cases, the transcript was not specified. Transcript type found in the cases is shown in Table 3.

The patients were risk stratified using three prognostic score systems – Sokal, Hasford, and EUTOS. There were some patients for whom risk stratification could not be done because of paucity of data which was depicted in Table 4.

The median duration of imatinib treatment before developing treatment resistance was 24 months (range: 3–60 months).

Based on the therapeutic response to imatinib, patients were categorized into primary and secondary failure taking into consideration the ELN guidelines. Both primary and secondary failures are subcategorized into hematological, cytogenetic, and molecular resistance. Categorization of imatinib failure is shown in Table 5. Of the 269 cases tested for imatinib resistance, mutations were detected in 88 (32.7%) cases and 181 (67.3%) cases were negative for mutations. The distribution of mutations

in primary and secondary failure was depicted in Table 6. Fisher's exact test did not result in statistical significance with  $P = 0.0536$ .

Mutations in kinase domain were detected in 88 (32.7%)

**Table 1: Baseline characteristics (n=269)**

Variable	Result
Median age in years (range)	36 (18-66)
Sex ratio, n (%)	1.7:1
Male	170 (63.2)
Female	99 (36.8)

**Table 2: Baseline hematological parameters**

Characteristic	Median (range)
Total leukocyte count, $\times 10^9/L$	180 (4.9-576)
Platelet count, $\times 10^9/L$	490 (100-1212)
Hemoglobin, g/dL	9.8 (5.5-15.4)
Peripheral blood blasts, %	3 (2-9)
Peripheral blood basophils, %	4 (2-16)

**Table 3: Molecular studies for BCR-ABL**

Transcript type	Number of cases
e14a2 (b3a2)	82
e13a2 (b2a2)	56
Transcript not specified	131

**Table 4: Risk stratification**

Risk	Sokal score, n (%)	Hasford score, n (%)	EUTOS score, n (%)
Low	36 (13.4)	42 (15.6)	142 (52.8)
Intermediate	110 (40.9)	118 (43.9)	NA
High	93 (34.6)	79 (29.4)	106 (39.4)
Data unavailable	30 (11.1)	30 (11.1)	21 (7.8)

NA – Not applicable; EUTOS – European Treatment and Outcome Study

**Table 5: Categorization of imatinib failure (n=269)**

Categories of imatinib failure	n (%)
Primary failure	70 (26)
Hematologic resistance	16 (5.9)
Cytogenetic and molecular resistance	54 (20.1)
Secondary failure	199 (74)
Hematologic resistance	89 (33)
Cytogenetic and molecular resistance	110 (41)

**Table 6: Mutation analysis and its distribution in imatinib failure**

Mutation category	Positive, n (%)	Negative, n (%)	Total
Primary failure	16 (18.2)	54 (29.8)	70
Secondary failure	72 (81.8)	127 (70.2)	199
Total	88 (32.7)	181 (67.3)	269

Fisher's exact test -  $P=0.0536$

cases. Mutations in ATP binding region (P-loop), other P-loop, substrate binding region, SH2 contact, A-loop, C-helix, and others were found in 28 (31.8%), 25 (28.4%), 14 (15.9%), 6 (6.8%), 3 (3.4%), 1 (1.1%), and 11 (12.5%) cases, respectively. In the ATP binding region, T315I mutation was seen in 28 cases (31.8%). Mutations in kinase domain based on the site and amino acid distribution were shown in Figures 1 and 2.

Of the 269 cases evaluated for imatinib resistance, the treatment was modified either as imatinib dose escalation or second-line TKI for 205 cases. The remaining 64 cases were given supportive care. Imatinib dose hike (600/800 mg), nilotinib, and dasatinib were given to 162, 30, and 13 cases, respectively. Response evaluation was done for these cases at 3 months and 12 months. Of 205 cases, 105 were in hematological failure at the time of treatment modification and the remaining 100 cases were in complete hematological response (CHR). These 105 cases were assessed for CHR at 3 months and were achieved in 53 of the 80 cases (66.2%) in imatinib dose hike, 13 of the 17 cases (76.4%) in nilotinib, and 6 of the 8 cases (75%) in dasatinib arms.

Molecular response was assessed in 187 of 205 cases. For 18 cases, molecular response could not be assessed at the end of 1 year of treatment modification. Molecular response (<1% of BCR-ABL) at 12 months was achieved in 37 of the 144 cases (25.7%) in imatinib dose hike, 14 of the 30 cases (46.6%) in nilotinib, and 7 of the 13 cases (53.8%) in dasatinib arms. Response to treatment modification is shown in Table 7.

Median OS (since imatinib resistance) for T315I mutation group was 20.5 months (range: 1.4–42.8 months), for P-loop mutation group was 31 months (range: 1.4–57 months), and it was not reached for the group with non-P-loop mutation (3.9 months-NR) and nonmutated groups (5.3 months-NR) with median follow-up of 48 months from the date of imatinib resistance (range: 1.4–96 months).

Four-year OS in mutation detected group was 37.5% and in nonmutated group was 87.7%. OS from the date of imatinib resistance was shown in Figures 3 and 4.

The hematological and nonhematological adverse effects were shown in Tables 8 and 9.

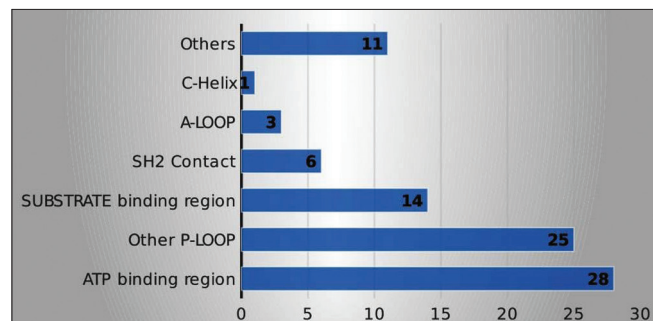


Figure 1: Mutations in kinase domain based on the site

## Discussion

Our study comprised 269 CML patients with imatinib treatment failure. The median age was 36 years (18–66 years) and the sex ratio was 1.7:1, whereas in other studies by Quintas Cardama Alfonso *et al.*,<sup>[17]</sup> Jabbour *et al.*,<sup>[18]</sup> Cortes *et al.*,<sup>[19]</sup> Rajappa *et al.*,<sup>[20]</sup> and Mishra *et al.*,<sup>[21]</sup> the median age was 52 years (18–79), 57 years (25–82), 51 years (17–96), 36 years (18–65), and

Table 7: Response to treatment modification

Drugs given after IRMA test (n=205)	CHR at 3 months - in hematological resistant group, n (%)	<1% BCR-ABL at 12 months, n (%)
Imatinib dose hike (n=162)	53/80 (66.2)	37/144 (25.7)
Nilotinib (n=30)	13/17 (76.4)	14/30 (46.6)
Dasatinib (n=13)	6/8 (75)	7/13 (53.8)

IRMA – Imatinib resistance mutation analysis; CHR – Complete hematological response

Table 8: Hematological adverse effects

Hematological Grade 3/4	Imatinib dose hike, n (%)	Nilotinib, n (%)	Dasatinib, n (%)
Anemia	48/162 (29.6)	3/30 (10)	2/13 (15.4)
Neutropenia	62/162 (38.3)	6/30 (20)	3/13 (23.1)
Thrombocytopenia	30/162 (18.5)	4/30 (13.3)	4/13 (30.7)

Table 9: Nonhematological adverse effects

Nonhematological all grades	Imatinib dose hike, n (%)	Nilotinib, n (%)	Dasatinib, n (%)
Peripheral edema	35/162 (21.6)	2/30 (6.6)	-
Skin rash	16/162 (9.9)	7/30 (23.3)	-
Nausea/vomiting	32/162 (19.7)	3/30 (10)	1/13 (7.6)
Diarrhea	21/162 (13)	2/30 (6.6)	-
Fatigue	48/162 (29.6)	3/30 (10)	2/13 (15.4)
Musculoskeletal pain	68/162 (42)	3/30 (10)	1/13 (7.6)
Headache	23/162 (14.2)	3/30 (10)	2/13 (15.4)

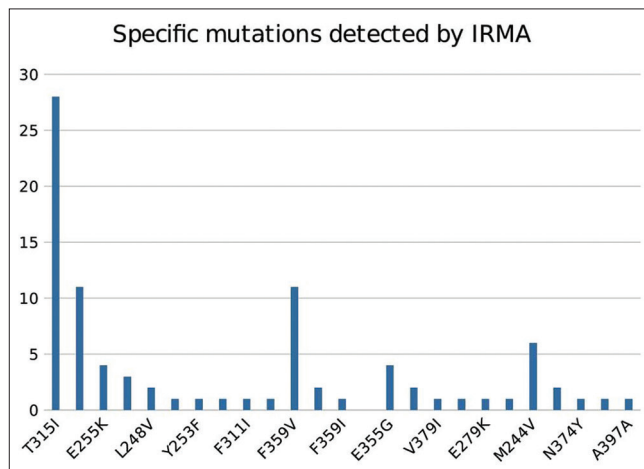
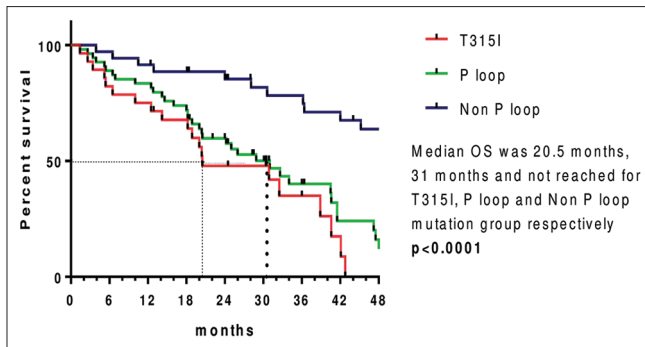


Figure 2: Mutations in kinase domain based on amino acid substitution



**Figure 3: Kaplan–Meier estimates of overall survival since imatinib resistance between various mutant groups**

35 years, respectively. The sex ratio was 1.08:1, 1.6:1, 2.7:1, and 1.6:1 in the studies done by Quintas Cardama Alfonso *et al.*,<sup>[17]</sup> Jabbour *et al.*,<sup>[18]</sup> Rajappa *et al.*,<sup>[20]</sup> and Mishra *et al.*,<sup>[21]</sup> respectively.

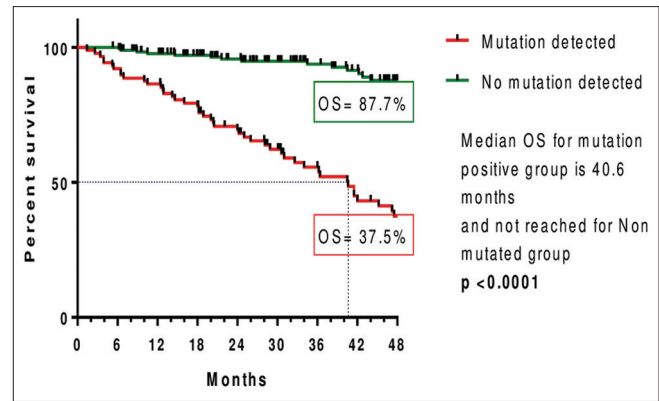
We stratified patients into different risk groups using three scoring systems; nevertheless, Sokal score was used in most of the studies<sup>[18,21,22,23]</sup> and in comparison to Western studies, this study had more number of intermediate and high-risk Sokal score.

In this study, the ratio of primary and secondary failure was 1:2.8 and the ratio of cytogenetic/molecular and hematologic failure was 1.57:1. The results of our study were similar to Jabbour *et al.*<sup>[18]</sup> which included all three phases of disease. Compared to our study, Jabbour *et al.*<sup>[23]</sup> showed higher cytogenetic failures. Rajappa *et al.*,<sup>[20]</sup> Cortes *et al.*,<sup>[19]</sup> and Kantarjian *et al.*<sup>[25]</sup> showed more hematological failures compared to our study.

However, Soverini *et al.*<sup>[24]</sup> showed similar ratio of hematological and cytogenetic failure when compared to our study, yet there is difference in the ratio of primary and secondary failure.

Although the frequency of mutations was higher in secondary failure cases, it was not statistically significant ( $P = 0.38$ ) in this study. Al-Ali *et al.*<sup>[26]</sup> and Soverini *et al.*<sup>[24]</sup> demonstrated significantly higher frequency of mutations in secondary failure cases. In the study by Jabbour *et al.*,<sup>[18]</sup> it was observed that mutations associated with secondary imatinib resistance occur more frequently in later stages of the disease and are associated with older age, prior interferon therapy, initiation of imatinib therapy in AP or BC, development of clonal evolution, high-risk Sokal score at diagnosis, and failure to achieve complete cytogenetic response (CCyR) by 12 months.

T315I was the most commonly seen mutation in our study (31.8%), Rajappa *et al.*<sup>[20]</sup> (31%) which was our previous institutional study and Suresh-Babu *et al.*<sup>[27]</sup> (16.6%) studies. IRMA was directed to T315I presence or absence for many years at our institute that could have been the reason for high proportion of this mutation in our study.



**Figure 4: Kaplan–Meier estimates of overall survival since imatinib resistance between mutated and nonmutated group**

E255 V/K mutation was the most common in Soverini *et al.*<sup>[24]</sup> study (16%) and it was seen in 5.7% of cases in our study. Quintas Cardama Alfonso *et al.*,<sup>[17]</sup> Jabbour *et al.*,<sup>[18]</sup> and Nicolini *et al.*<sup>[22]</sup> showed the most frequent mutation at G250 residue and this was the 3<sup>rd</sup> most common in our study and Rajappa *et al.*<sup>[20]</sup> and Srivastava and Dutt<sup>[31]</sup> studies.

#### **Treatment modification after imatinib resistance mutation analysis result**

In our study, CHR at 3 months to imatinib dose escalation was 66.2%. In various studies on imatinib dose escalation, the CHR at 3 months was between 45% and 86%.<sup>[23,25]</sup> In our study, CCyR/<1% of BCR-ABL at 12 months after imatinib dose escalation was 25.7% of cases. In other studies, it is between 17.5% and 59.5%.<sup>[20,23,25]</sup>

For 2<sup>nd</sup>-line TKI, CHR at 3 months was attained in 75% of cases in our study. In other studies,<sup>[17,19,28-30]</sup> CHR at 3 months ranged from 82% to 92%. In this study, CCyR/<1% of BCR-ABL at 12 months to 2<sup>nd</sup>-line TKI was 46.6% to nilotinib and 53.8% to dasatinib. In other studies, it ranged from 28.4% to 69%.

#### **Survival analysis**

In this study, the median OS and range for T315I mutation and P-loop mutation were 20.5 months (range: 1.4–42.8) and 31 months (range: 1.4–57), respectively, and it was not reached for the group with non-P-loop mutation (3.9 months-NR) and nonmutated groups (5.3 months-NR). The 4-year OS in mutation-detected group was 37.5% and in nonmutated group was 87.7%.

Our study showed inferior survival for T315I and P-loop mutation patients compared to those with non-P-loop mutations and with no mutations. Similar results were seen in the study done by Nicolini *et al.*<sup>[22]</sup> There was no difference in survival between patients with T315I, other mutations, or no mutations in the study done by Jabbour *et al.*<sup>[30]</sup>

In this study, the 4-year OS was inferior in the group with mutations compared to the group with no mutations. Results were similar in the studies done by Quintas Cardama Alfonso *et al.*<sup>[17]</sup> and Nicolini *et al.*<sup>[22]</sup>

### Limitations of the study

The drawbacks of this study were that it is retrospective study. Laboratory data were not available for all patients to stratify the risk. There was underreporting of both hematological and nonhematological adverse events because of inadequate documentation in case records. Second-generation TKI and hematopoietic stem-cell transplantation could not be provided for the eligible cases due to financial constraints.

### Conclusion

Imatinib-resistant mutations were more common in the cases with secondary failure though it was not statistically significant. T315I mutation which is resistant to all second-generation TKIs was the common mutation found in the study.

Imatinib dose hike to the failure cases resulted in optimal hematological response rates which is on par with second-generation TKIs.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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