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Distribution of ABL Kinase variant analysis to Imatinib Resistance in Different Subsets of BCR ABL1 Chronic Myeloid Leukemia in major tertiary care hospital in Pakistan

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INTRODUCTION

Imatinib mesylate is a potent and selective inhibitor of the oncogenic BCR-ABL tyrosine kinase, which is deregulated in as many as 95% of chronic myeloid leukemia (CML) patients and in ~20% of adult Philadelphia-positive (Ph+) acute lymphoblastic leukemia (ALL) patients. Despite its striking efficacy, however, resistance is observed in a proportion of patients, especially those with Ph+ ALL or advanced-stage CML. The most important mechanism that may confer imatinib resistance is point mutation within BCR::ABL kinase domain. Other generation ABL tyrosine kinase inhibitors such as dasatinib, nilotinib, bosutinib and ponatinib help to overcome imatinib resistance . Sensitivity of the patient to each of the above TKIs depends upon the individual candidate mutation present. Thus, it is important to perform mutation analysis for effective therapeutic management of CML patients once they show imatinib resistance. We used direct sequencing to identify the different types of mutations responsible for resistance of imatinib treatment from across the Pakistan in single tertiary care hospital

AIM

Imatinib mesylate is a potent and selective inhibitor of the oncogenic BCR-ABL tyrosine kinase, which is deregulated in as many as 95% of chronic myeloid leukemia (CML) patients The most important mechanism that may confer imatinib resistance is point mutation within *BCR::ABL* kinase domain. Thus, it is important to perform mutation analysis for effective therapeutic management of CML patients once they show imatinib resistance. We used direct sequencing to identify the different types of mutations responsible for resistance of imatinib treatment from across the Pakistan in single tertiary care hospital

METHOD

This retrospective observational study was conducted at the Section of Molecular Pathology, Aga Khan University Hospital, Karachi, Pakistan. Over a period of 2 years (from January 2022 to December 2023). In this study, the patient resistance for the imatinib were analyzed for BCR: ABL1 kinase domain mutation by direct sequencing and the detected mutations along with their percentage prevalence were reported. Total RNA is extracted from blood or bone marrow aspirate, followed by cDNA conversion and PCR amplification. Amplified DNA is sequenced by Sanger sequencing. Interpretation of sequencing data is performed using Mutation Surveyor software.

RESULTS

Out of the tested 165 patients, male comprised 54% of the total while females were 46 % included in the full analysis. The median age was 39 years (range, 14-83 years). 165 patients with CML were analysed for *BCR:ABL* kinase domain mutation. Total 58 (35 %) patients out of 165 had mutation in at least one of the domains of *BCR:ABL* conferring resistance to different generations of TKI. Mutations in *BCR:ABL* kinase domain was observed in different domain of *BCR::ABL*. ATP binding P-Loop[E255K,Y253H,G250E,L248V and M244V (41 %), A-Loop [A397P](3%), SH2 contact[F359C,E355G & F359I/V] (28%) and SH3 contact [T315I, F311I] (28 %)

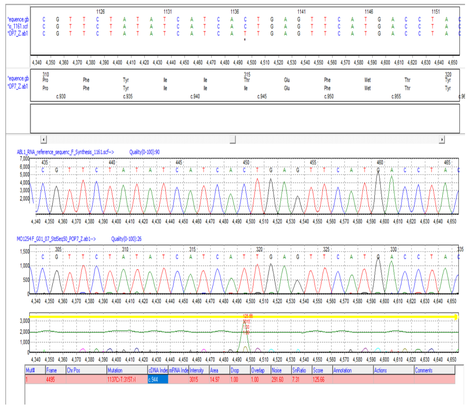


Figure.1. Results of mutational screening by sequence analyses revealing the T315I mutation in the ABL kinase domain. Direct sequencing to detect the mutation in the ABL kinase domain in Patient sample

Structural motifs within the Kinase domains	Mutations	Variant prevalence	CML Phase
ATP binding P-Loop	E255K,	10	Chronic Phase=35
	Y253H,	10	Accelerated Phase=3
	G250E,	12	Blast Phase=01
	L248V	2	
	M244V	5	
A-Loop	A397	3	Chronic Phase=03
SH2 contact	F359C,	7	Chronic Phase=24
	E355G	2	Accelerated Phase=02
	F359I/V	7/12	Blast Phase=02
SH3 contact	T315I,	26	Chronic Phase=20
	F311I	2	Accelerated Phase=05
			Blast Phase=03

Table.1. Variant prevalence among structural motifs within the kinase domain mutations

CONCLUSIONS

We conclude that (*a*) amino acid substitutions at seven residues (T315I,G250E, Y253H, E255K,F359V and F359I) account for 77% of all resistance-associated mutations and (*b*) the presence of either P-loop or T315I mutations in imatinib-treated patients should warn the clinician to reconsider the therapeutic strategy

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