Mutation analysis of ABL kinase domain in Tunisian CML patients treated with tyrosine kinase inhibitors

Rim Frikha; Amina El Aoud; Hassen Kamoun
Genetic Department, University hospital of Sfax, Tunisia

INTRODUCTION

The most common mechanism for reactivating the kinase activity of the BCR-ABL gene is point mutations within the ABL kinase domain (ABL/KD). These mutations have been linked to clinical resistance to tyrosine kinase (TK) inhibitors in chronic myeloid leukemia (CML) patients, which is associated with poor prognosis.

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. Consequently, conducting mutation analysis is crucial for the effective therapeutic management of CML patients exhibiting imatinib resistance.

AIM

This study was carried out to assess the prevalence and clinical impact of ABL/KD mutation in Tunisian CML patients

Kinase Domain Mutations

TKI	Contraindicated Mutations
Dasatinib	T315I/A ; **F317L/V/I/C ; V299L**
Nilotinib	T315I , Y253H ; E255K/V ; G250E
Bosutinib	T315I ; V299L ; G250E ; F317L
Ponatinib	**Compound Mutations**

METHOD

A retrospective study was carried out in the Hospital University of Sfax, south of Tunisia. CML patients were enrolled in this study.

Quantitative assessment of the BCR-ABL transcript was performed using the Cepheid Xpert BCR-ABL ultra-assay to assess molecular response , according to the European Leukemia Net guidelines,

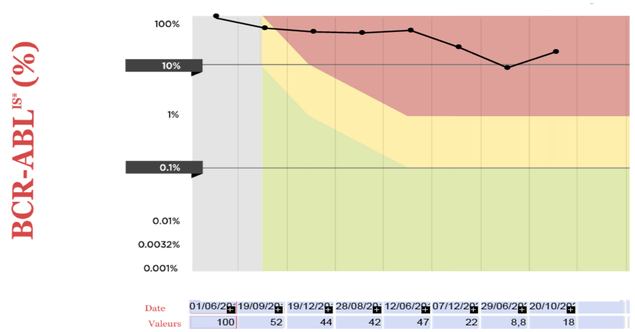
A Sanger sequencing was performed using a high-fidelity DNA polymerase.

CONCLUSIONS

Our results highlight that ABL/KD mutation are uncommon in Tunisian CML patients, and delineation of landscape of resistance is mandatory for early detection of emerging mutant clones which may help in decision-making for alternative treatment.

RESULTS

Thirty-nine patients with confirmed CML were enrolled in this study. the median age was 57 years, and the sex ratio M/F was 1.2. According to the ELN criteria, Optimal and resistance were noted in 18(46.2%) and 21 (53.8%) patients; respectively. None of the ABL/KD mutations were detected.



Minimal residual disease in TKI- resistant CML patient

CONTACT INFORMATION

Pr. Rim Frikha MD/PhD
Histology-embryology & molecular genetics in onco-hematology
Faculty of Medicine & Genetic's department at the university hospital of Sfax –Tunisia;
Email: frikha_rim@yahoo.fr.

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