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Spectrum of BCR-ABL Kinase Domain Mutations in North Macedonia in Patients With CML Resistant to Imatinib

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INTRODUCTION

Most patients treated with first-line tyrosine kinase inhibitor (TKI) imatinib achieve durable response but may lose the response at some point during treatment. ***The most important mechanism behind imatinib resistance is the appearance of a mutation within the BCR::ABL kinase domain***. Mutation analysis is usually performed after patients experience resistance to TKI treatment and the results of mutation analysis is important in the selection of the next TKIs. ***Emergence of new mutations during imatinib treatment predicts loss of CCyR, shorter progression-free survival, shorter time to BC progression, and shorter OS.*** Patients that already have mutations have higher chance of developing new mutations and also multiple mutations are associated with poor prognosis.

AIM

The aim of this study is to ***determine the types of most common BCR-ABL mutations in North Macedonian*** patients with CML resistant to imatinib and their clinical characteristics.

METHOD

This is a ***retrospective descriptive analysis*** of data obtained from medical records of patients with CML resistant to imatinib treated at University Clinic for Hematology, Skopje.

The study collected data from patients with CML treated at the Clinic for Hematology, Skopje in the period between January 2018 and December 2023.

Mutation screening for BCR-ABL1 KD was performed in CML patients who showed resistance to imatinib treatment and loss of hematological od molecular response to Imatinib. Evaluation of mutation were made from examples of peripheral blood – with method of sanger sequencing on cDNA (duplex sequencing).

RESULTS

A total of 194 cases of CML were reviewed, and 35 cases (18%) of failure to the initial therapy were found. A total of **17 patients (49%) out of 35** had a mutation in at least one of the domains of BCR: ABL.

Fifteen different types of mutations were detected. The types of mutations by region of occurring noticed in the patients were **P-loop, C-loop, SH2 contact, SH3 contact, low-frequency mutations and contact binding site.**

Mutations occurring in :

- the contact binding site region: **T315I;**
- P-loop: **M244V; Q252H; L248V; M237V; E255K; G250E; Y253H;**
- SH-2 domain: **F359V; F359I; E355G;**
- SH3 domain: **E279G;**
- C-loop: **F281K;**
- Low frequency mutations: **E459V; K222E.**

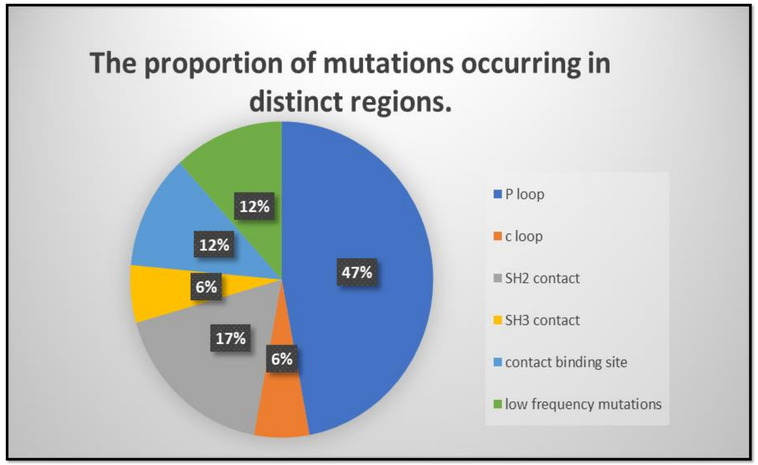
The most common mutation was E355G, noticed in 3 patients (18%). The second most common mutations were M244V and T315I, seen in 2 patients (12%). *One of the patients had 3 different mutations: T315I, E279G, and M244V.*

Table1. Clinical and hematological characteristics of the patients with mutations at the time of diagnosis

	Total 17 patients
Sex	
Male	11
Female	6
Age	Mean 53 years (range 20-78 years)
Spleen	
Normal	10
Splenomegaly >12cm	7
Hb	
Normal (120-160 g/L)	10
Anemia (<119 g/L)	7
Platelets	
Normal 150-450 (10^9 /L)	9
Thrombocytopenia < 150(10^9 /L)	2
Thrombocytosis > 450 (10^9 /L)	6
WBC	
Leucocytosis > 9 (10^9 /L)	17
Normal count of WCB	0

The **median age at diagnosis was 53 years**, and **42% had splenomegaly** at initial presentation. In the group of patients with mutations, 11 (65%) were men and 6 (35%) were women

Chart 1. Proportion of mutations occurring in distinct regions



The types of mutations were ATP-binding P-loop 47 % (8), C-loop 6% (1), SH2 contact 17% (3), SH3 contact 6.6% (1), and low-frequency mutations in 13.3% (2) , and contact binding site region mutations 12% (2) of patients.

Overall, 11 patients (65%) were alive with complete hematologic response, whereas 6 patients (35%) had died at the time of evaluation.

CONCLUSIONS

Point mutations were frequently detected in patients resistant to imatinib. A total 49% of patients (17/35) show mutation in at least one of the BCR-ABL kinase domain. *This contributes to the choice of another generation TKI therapy and emphasizes the need for BCR-ABL gene sequence analysis to detect the mutations in CML patients in order to properly guide the therapy.*

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