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Frequency, distribution, and impact on prognosis of *BCR-ABL1* kinase domain mutations in tyrosine kinase inhibitor resistant chronic myelogenous leukemia patients

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Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative disease characterized by the *BCR::ABL1* fusion gene. Despite the improved outcomes with the tyrosine kinase inhibitors (TKIs) treatment, primary and acquired resistance has become a big challenge. Through the various mechanisms, *ABL1* tyrosine kinase domain (TKD) mutations play a major role in the resistance. Of the 287 patients in our study, 261 patients' resistance status were available, and 110 (42.2%) were resistant to imatinib (IM). Ninety of those 110 patients' *BCR-ABL1* TKD mutation analyses were available, and 13 of them (14.4%) had mutations. 8 of them had the T315I mutation, 2 had the Y253H mutation, and the remaining patients had one E255K, V299L, and F317L mutation each. In the IM-resistant patients, the mean size of the spleen was larger, peripheral white blood cell count and plasma β2-microglobulin levels were higher, and hemoglobin and hematocrit levels were lower ($p<0.05$). Also, it could not be detected any significant correlation between fusion signal patterns and the rate of IM resistance. In conclusion, *ABL1* TKD mutations are essential causes of TKI resistance in CML patients and must be used to choose the appropriate subsequent TKI.

Keywords: chronic myeloid leukemia, IM resistance, ABL1 TKD mutations

1. Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic disorder characterized by the fusion of the BCR and ABL1 genes. BCR::ABL1 fusion gene encodes a chimeric oncoprotein with abnormally high and constitutive tyrosine kinase activity (1). Aberrantly activated kinase causes enhanced proliferation and differentiation arrest (2). Clinical signs and symptoms are seen due to differentiation arrest and accumulation, including fatigue, and a loss of appetite, granulocytosis, granulocytic immaturity, basophilia, thrombocytosis, and splenomegaly (1).

Chronic myeloid leukemia has three distinct clinical stages: chronic phase, accelerated phase, and blast crisis. Without treatment, the disease progresses from chronic phase to accelerated and blastic phase, resulting in death within an average of 4 years (2). Targeted therapies using tyrosine kinase inhibitors (TKIs) have drastically improved life expectancy (3). Imatinib was the first TKI introduced, and it increased the 5-year survival rate from 22% to 70% compared to pre-imatinib. Treatment fails in some patients, and several TKIs, including dasatinib, bosutinib, nilotinib, ponatinib, and asciminib, have been introduced to overcome this resistance (4). TKD mutations are well-known causes of TKI resistance and have the potential to direct treatment (5). Different methods with advantages and disadvantages have been used to detect TKD mutations, and different mutation frequencies and distributions have been determined so far among studies (6, 7).

The present study aims to assess the frequency and distribution of BCR::ABL1 TKD mutations in TKI-resistant CML patients.

2. Materials and Methods

2.1. Patients

We examined a group of BCR::ABL1 TKD mutations in 93 imatinib-resistant patients. Among the 287 consecutive CML patients followed by Ondokuz Mayıs University Faculty of Medicine between January 2008 and March 2017, TKI-resistant patients were enrolled in this study. The age, gender, blood cell count, plasma LDH and β2-microglobulin levels, TKIs used, survival rates, BCR::ABL1 fusion patterns detected with FISH and BCR::ABL1 TKD mutation results were collected.

2.2. BCR-ABL Fusion Detection with FISH and RT-qPCR Methods

FISH (fluorescence in situ hybridization) analyses were conducted with Dual Color, Dual Fusion Translocation Probes provided by either Vysis or Cytocell companies (Vysis,

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Downers Grove, IL; Cytocell, Cambridge, UK).

BCR::ABL1 fusion transcript quantification was performed with RT-qPCR (Reverse transcription-quantitative polymerase chain reaction) analysis by Roche LightCycler BCR-ABL1 or Ipsogen BCR-ABL1 Mbcr IS-MMR kits. Total RNA was extracted from peripheral blood using the QIAamp RNA Blood Mini Kit. Then, cDNA was obtained using an ipsogen RT Kit, and the quality of synthesized cDNA was checked by cDNA-PCR amplification of wild-type ABL1 housekeeping gene. For the quantification of BCR-ABL1 Mbcr fusion gene transcripts, Ipsogen® BCR-ABL1 Mbcr kit was used according to the manufacturer's recommendations.

2.3. Sequencing Analysis of BCR::ABL1 TKD Mutations

Pyrosequencing of the eleven targeted mutations provided below was performed on Qiagen Q24 Pyromark. The PCR products obtained for the RT-qPCR mentioned above study were used as input material and pyrosequencing was performed with four different primer pairs to detect specific mutations: Primer Pair-1: Y253H, Y253F, E255K, E255V; Primer Pair-2: V299L; Primer Pair-3: T315A, T315I, F317V, F317L; Primer Pair-4: F359C, F359V. Sequencing results were analyzed with Pyromark Q24 software.

2.4. Statistical Analysis

Statistical analyses were performed using IBM SPSS Version 22.0 (SPSS, Chicago, USA). The Mann-Whitney U test and Student's t-test were used to compare the differences between the groups. Kaplan-Meier and log-rank tests were used for survival analysis. P-value <0.05 was considered as significant.

3. Results

3.1. Patient characteristics

A total of 287 consecutive CML patients, 143 females and 144 males, were enrolled in this study, and patients' characteristics were summarized in Table 1. Two hundred sixty-one patients' follow-up information was available. One hundred ten (42.2%) of the 261 patients were resistant to TKI.

The mean overall survival of the cohort was 177.5 months, and IM-resistant patients had shorter overall survival (139.5 months vs 206.6 months; Log-rank p<0,05). Analysis of baseline clinical findings is presented in Table 2. Imatinib-resistant patients' mean spleen size (181.8 vs. 153.0 mm), white blood cell count (153.2 vs. 104.3 x10^9/L), and ß2-microglobulin level (3,040 vs. 2,581 ng/mL) were significantly higher, and hemoglobin levels (10.7 vs. 11.5 g/dl) were lower than the imatinib-sensitive patients' (p<0.05) (Table 2).

Table 1. Characteristics of patients cohort

Sex	
Female/Male	143/144
Age of onset (mean+SD)	52.5±17.3
FISH fusion patterns	
2F1G1R (dual fusion)	178
1F1G1R (deletion of BCR and ABL1)	21
1F2G1R (deletion of ABL1)	10
1F2G2R (complex translocation)	8
3F1G1R (*+Ph*)	3
1F1G2R (deletion of BCR)	2
2F2G2R	2
N/A	63
Imatinib response status	
Sensitive	151 (%52.6) (57.8%)
Resistant	110 (%38.3) (42.2%)
No follow-up	26 (9.0%)
Phase in Resistant group	
Accelerated phase	7
Blastic phase	16
Chronic phase	87
***BCR::ABL1* TKD mutation**	
Yes	13
No	77
N/A	20

Table 2. Comparison of the baseline clinial features of IM-resistant and IM-responsive patients

	Resistant	Responsive
Onset Age	50±18,5 yrs	53±16.2 yrs
Liver size (mm)	181.2±25.9	178.7±25
Spleen size (mm)	181.8 ±61.1	153±41.2*
WBC (x10^9/L)	153.2±136	104.3±85.9*
Hemoglobin (g/dL)	10.7±2.1	11.5±2.1*
Hematocrit (%)	32.2±6.2	35.4±6.2*
Thrombocyte (/dL)	430,153±322,002	497,983±353,318
ESR (mm/h)	28.8±27,1	20.2±21.9
LDH (U/L)	987.6±586.6	903.8±647.7
B2M (ng/mL)	3,040.1±1,513.7	2,581.5±914*

WBC: White Blood Cell, ESR: Erythrocyte Sedimentation Rate, LDH: Lactate DeHydrogenase, B2M: β2 microglobulin, yrs=years * p < .05

3.2. FISH Analysis Patterns at Baseline

FISH analysis patterns for BCR::ABL1 with dual fusion probes at diagnosis were available for 224 patients. Results are depicted in Table 1. 79.5% (178/224) of the patients had classical dual fusion (2F1G1R), and the remaining 20.5% (46/224) had various fusion patterns. Of the 46 patients, 21 patients (45.7%) had 1F1G1R (loss of derivative 9), ten patients (21.7%) had 1F2G1R (deletion ABL1), eight patients (17.4%) had 1F2G2R (complex variant translocation), three patients (6.5%) had 3F1G1R (additional Ph), two patients (4.3%) had 1F1G2R (deletion BCR), two patients (4.3%) had 2F2G2R. The mean age of diagnosis of the patients with FISH fusion patterns other than dual fusion was earlier than the patients with classical dual fusion FISH patterns (54.3±17.7 vs 48.2±15.2 years; p<0.05), but no statistical difference was detected between the classical fusion pattern and the other group in terms of imatinib resistance rate (44.7% vs 54.5%; p>0,05) and overall survival (154.3 months vs. 117.4 months, log-rank p=0.8).

3.3. BCR::ABL1 TKD Mutation Analysis

Among the 110 imatinib-resistant patients, the mutation status of 90 imatinib-resistant patients could have been assessed, and 13 (14.4%) patients had mutations in the BCR::ABL1 TKD (Table 3). T315I was our study's most common mutation, and the detected mutations are depicted in Fig. 1. T315I was detected in 8 patients, Y253H in 2 patients, and E255K, V299L, and F317L mutations were detected in one patient each. Of the 13 patients with the mutation, 7 (36,8%) were in the accelerated/blastic phase. The BCR::ABL1 TKD mutations were clustered statistically significantly higher in patients with accelerated/blastic phase (36.8% vs 8.4%; $p<0.05$). Patients with Y253H and E255K were also resistant to subsequent nilotinib treatment, V299L and F317L were also resistant to subsequent dasatinib treatment, and patients with T315I mutation were resistant to both dasatinib and nilotinib treatments. We also investigated whether there was a relationship between BCR::ABL1 TKD mutation carriers and FISH fusion pattern types among IM-resistant patients and found no significant differences.

Table 3. Type and frequency of *BCR::ABL1* TKD mutations among Imatinib-resistant patients with CML

Mutations	Frequency	Percent
Presence of mutations		
Yes	13	14.4
No	77	85.6
Type of TKD mutations		
P-loop mutations		
Y253H	*2*	2.2
E255K	1	1.1
Non-P-loop mutations		
V299L	1	1.1
T315I	8	8.9
F317L	1	1.1

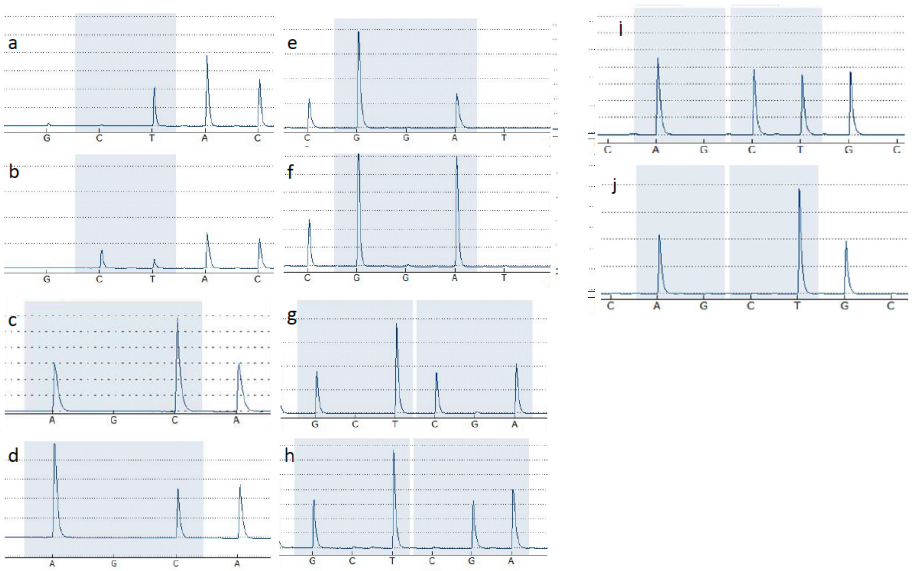

Fig. 1. Pyrosequence images of the patients with certain BCR-ABL1 TKD mutations and wild type control. a. Y253H wild type b. Y253H (TAC>CAC) mutant c. V299L wild type d. V299L (ACC>AAC) mutant e. E255K wild type f. E255K (GGA>GAA) mutant g. F317L wild type h. F317L (TTC>TTG) mutant i. T315I wild type j. T315I (ACT>ATT) mutant

4. Discussion

Tyrosine kinase inhibitors have caused significant advances in the treatment of CML and have improved the overall survival of patients considerably. However, some patients do not respond to the treatment initially or develop TKI resistance over time. For patients with CP-CML, imatinib achieves a major molecular response (MMR) in 50%-60% of cases. Following the literature, our study found the MMR rate to be 57.8% (8). Two of the most extensive studies, IRIS and DASISION, appear to have very different results on the MMR rate. However, when the IRIS study, in which the rates were low, was carefully examined, it could be recognized that approximately 20% of the patients needed follow-up. Therefore, the rates might be lower (9, 10). IM resistance also affects the overall survival of CML patients. In a recently published comprehensive study, IM-resistant patients had a shorter 3-year OS than IM-responsive patients, which is consistent with our results (11).

Although many causes of imatinib resistance have been identified, the most important is BCR::ABL1 gene TKD mutations. Mutation rates vary widely across studies, between 10.3% and 63%, depending on the selection criteria for mutation analysis and the method used. Mutation rates were 11.6% and 10.3% regardless of resistance status in two studies conducted with Sanger sequencing. In studies conducted with Sanger sequencing analysis on resistant patients, quite different results were obtained, ranging from 22.4% to 63% (12, 13). Although highly variable mutation rates, 10.5-45%, have been reported in the literature, most studies fell in 10-20%. In this study, we analyzed a group of targeted mutations among the IM-resistant patient group and found the rate to be 14.4%, consistent with the literature. The most common mutation was

T315I, and the mutation distribution was similar to that in the literature (8). BCR::ABL1 TKD mutation type is essential for choosing subsequent treatments. T315I mutation has been associated with both nilotinib and dasatinib treatments, Y253H and E255K mutations have been associated with nilotinib treatments, and V299L and F317L mutations have been associated with dasatinib treatments in the literature. Our patients' data were also consistent with the literature.

Predicting the prognosis of the disease at diagnosis is essential for the management and follow-up of the treatment. The age at diagnosis, spleen size, blast count, eosinophil, basophil percentages, platelet count, and chromosomal abnormalities are well-defined parameters for prediction. This study examined these parameters among the imatinib-resistant and -sensitive patients. Compared to imatinib-sensitive patients, the imatinib-resistant patients showed higher leukocyte counts and β2 microglobulin levels, larger splenic sizes, and lower hemoglobin levels at diagnosis. These findings were also following the literature data (14, 15).

It has also been suggested that the type of FISH fusion patterns could be used to predict IM resistance. These patterns could be the signifier of dual fusion patterns, deletion of chromosome 9q or chromosome 22q on the fused chromosome, loss of whole fused chromosome 9, additional Philadelphia chromosome, and complex translocations related to BCR and ABL1. In the literature, the percentage of fusion patterns other than dual fusion ranged from 9.2% to 28.5% (16-18). Our study found that the rate within this range and the distribution of the patterns were also consistent with the literature. Few studies have been carried out on the prognostic significance of this derivative chromosome structure, and contradictory results have been obtained. Early reports in the IM era revealed that in the deletion group, complete hematological response rate, progression-free survival, and MMR were lower (19, 20). However, subsequent studies (21-23) found no difference in survival and remission rates between the deletion and the non-deletion groups. Our study was consistent with these literature data.

One of the most striking FISH groups is variant translocations. El-Zimaity (24) found that patients with variant translocations showed similar response rates and survival times. Also, no significant differences were found regarding white blood cell and platelet counts and hemoglobin levels. Many other studies have shown that patients with variant translocations do not differ prognostically. However, variant translocation has been associated with poor prognosis in some studies. In our study, the number of patients with complex translocation is inadequate for a good comparison, but there was no statistically significant difference among groups.

This study had some limitations related to the incomplete data for initial prognosis assessment and clinical failure. Clinical prediction scores like Sokal, ELTS, and EUTOS could not be calculated due to incomplete data like blast percentage at the diagnosis. Also, our study had various advantages and significant disadvantages due to the mutation analysis method. We were able to analyze only a limited number of mutations.

In conclusion, the most critical challenge in treating CML is the development of TKI resistance, which is seen in many patients. Predicting the prognosis of patients at the time of diagnosis and identifying the BCR::ABL1 mutation type in resistant patients could guide the subsequent treatment and improve patient care. New techniques like high-throughput sequencing can identify more mutations, and different mechanisms that lead to imatinib resistance will be identified. This could pave the way for treatments that can be used to care for patients with CML and overcome resistance.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: O.S.A., G.O., M.T., Design: O.S.A. G.O., Data Collection or Processing: O.S.A, M.T., D.O., Analysis or Interpretation: O.S.A, G.O. E.A, Literature Search: O.S.A., E.K., U.A., Writing: O.S.A., U.A.

Ethical Statement

The study was approved by the ethics committee of the Faculty of Medicine of Ondokuz Mayıs University (approval date 05.05.2017 and file number B.30.2ODM.0.20.08/916). Written informed consent was obtained from all patients.

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