CML-558

NGS Reveals Key Genetic Variants in 51.1% of TKI-resistant CML Patients.

Genetic Alterations in Chronic Myeloid Leukemia Patients With Tyrosine Kinase Inhibitors Resistance From Guatemala Through Next-Generation Sequencing.

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INTRODUCTION

BCR::ABL1-positive patients with chronic myeloid leukemia (CML) are treated with tyrosine kinase inhibitors (TKIs) to reduce the transcript copy-number, achieving a major molecular response. However, genetic alterations in *ABL1* and other genes may be associated with resistance, highlighting the importance of characterizing genetic abnormalities in patients.

AIM

To determine the existence of additional genetic alterations in *BCR::ABL1*-positive CML patients with TKI resistance in Guatemala.

METHOD

45 CML, *BCR::ABL1*-positive patients with TKIs resistance according to the European LeukemiaNet (ELN) recommendations were selected.

Next-generation sequencing was conducted from 2021 to 2023.

A commercial 30-gene somatic panel was used for the analysis.

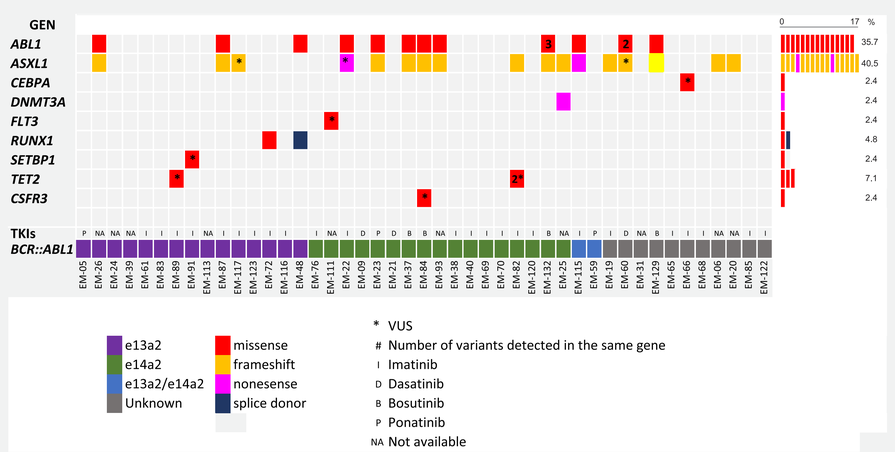
Variants were classified based on the AMP guidelines, ASCO, CAP, and ClinVar.

Table 1. Clinical information of TKI-resistant CML patients

	n	%
Sex		
Male	22	49.0%
Female	23	51.0%
Age		
Male	34.5 (18-64)	
Female	43 (23-73)	
Age of diagnosis		
Male	30 (15-60)	
Female	36 (19-73)	
Type of *BCR::ABL1* fusion		
e13a2	15	33.3%
e14a2	17	37.8%
e13a2/e14a2	2	4.4%
Unknown*	11	24.4%
Range *BCR::ABL1* IS%	1.68 - *BCR::ABL1>ABL1*	
Reached MMR at some point of therapy		
Yes	18	40.0%
No	27	60.0%
TKI at NGS		
Bosutinib	4	9.0%
Dasatinib	3	7.0%
Imatinib	25	56.0%
Ponatinib	3	7.0%
NA	10	22.0%
Patients with variants		
Negative	22	48.89%
Positive	18	37.77%
VUS	5	13.33%

IS: International Scale for reporting *BCR::ABL1* transcript.
NA: Not available.
*Patiens were positive for p210, but no molecular fusion classification was performed.

Figure 1. Genetic variants detected in TKI-resistant CML patients



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RESULTS

Patients were distributed proportionally by sex, and the average age of diagnosis was 35 years old (Table 1).

We detected 42 variants in 23 (51.1%) patients. Eighteen (40%) had pathogenic variants in one or multiple genes, whereas only 5 had variants of uncertain significance.

We identified 31 pathogenic variants in 4 genes. The most frequent variants were found in *ABL1* (15/31), *ASXL1* (13/31), *RUNX1* (2/31), and *DNMT3A* (1/31).

All *ABL1* variants were missense variations occurring in the kinase domain, whereas *ASXL1* were frameshift variants located within exon 13. *RUNX1* exhibited splice donor and missense alterations both in exon 4. The only *DNMT3A* alteration was nonsense in exon 15 (Figure 1).

CONCLUSIONS

Despite the limited number of patients, our results showed that 51.1% of our patients presented a variant in *ABL1* or other myeloid-related genes.

The ELN and other studies[1,2] have reported variants in *ABL1* and in epigenetic regulator genes such as *ASXL1*, *RUNX1*, and *DNMT3A*.

Our population shows a lower average age of diagnosis compared to other studies which consequently turns into a younger population with TKIs resistance[3,4]

Concerning this presentation, the presenter declares no conflicts of interest.

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