Recent Perspective of Next-Generation Sequencing (NGS) in Non-*BCR::ABL* Mechanisms of Resistance in Patients With Chronic Myeloid Leukemia

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Background

Although tyrosine kinase inhibitors (TKIs) have successfully been used to treat CML, some patients develop therapy resistance. Most resistance is due to mutations in the tyrosine kinase domain of *BCR::ABL*. However, there are still many cases with unknown causes of resistance to TKIs.

Objective

Determine *BCR::ABL*-independent biomarkers of resistance to TKIs in patients with CML using NGS.

Materials & Methods

This study included 24 patients (12 men and 12 women) with a median age of 43 years (IQR 26–72 years) with CML resistant to TKI therapy. The control group was 5 patients (3 men and 2 women) with a median age of 54 years (IQR 33–72 years) with CML and optimal response (MMR) to TKI.

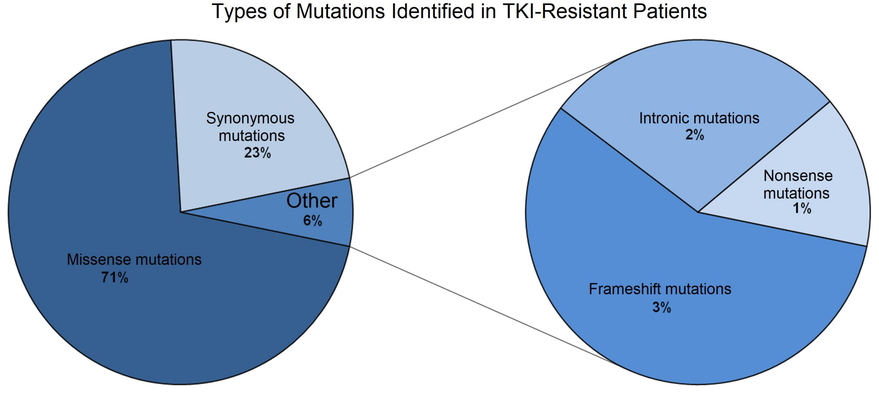
A myeloid panel of 116 genes with an average reading depth of 200× or 1000× on MiSeq (Illumina) was used. The clinical significance of mutations was evaluated using COSMIC, ClinVar, and VarSome.

References

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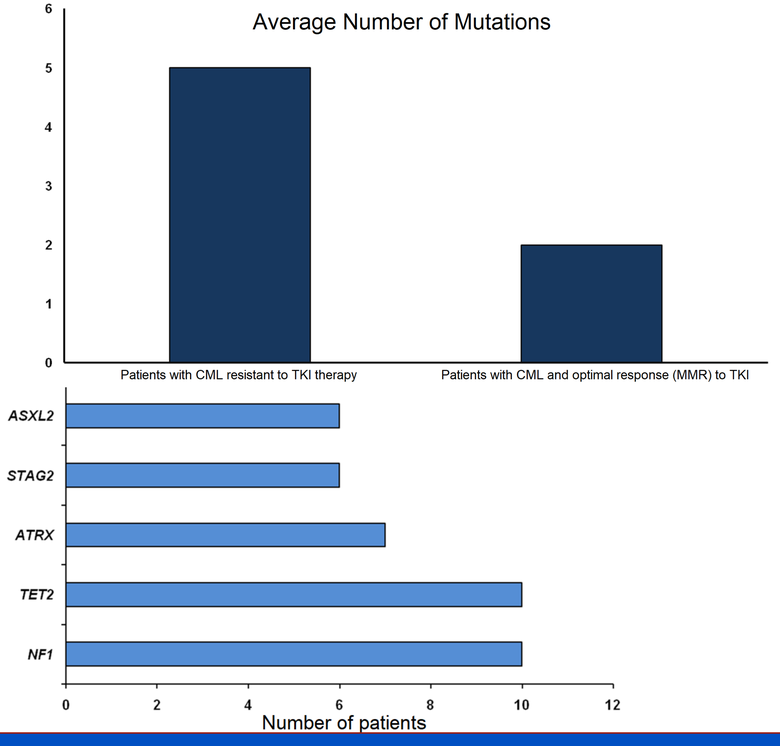
Results

All studied patients were found to have genetic abnormalities. However, more mutations were detected in the group of patients with resistance than in the control group (average of 5 and 1 mutations, respectively). Multiple mutations were detected in 63% of patients with resistance, although 92% of these mutations had unclear clinical significance. The most common abnormalities were found in tumor suppressor *NF1* (10/24), transcription regulators *TET2* (10/24) and *ATRX* (7/24), cohesin complex member *STAG2* (6/24), and epigenetic regulator *ASXL1* (6/24). Mutations were also found in the intron region of *BCR* (2/24). Two patients had pathogenic mutations in *ASXL1* (p. G646Wfs*12), which could cause TKI resistance. Despite mutations in *NF1* and *ATRX* being more common in treatment-resistant patients, in our study, these mutations were also noted in optimal responders.



Summary

The detection of multiple mutations in patients with CML may explain resistance to TKI therapy; however, to better understand the pathogenesis of CML, it is important to know not only the presence of certain mutations but also their level of expression and to study the effects of various regulatory elements, such as transcription factors and miRNAs.



The work was performed at the Research Center for Cellular and Molecular Pathology of Russian Research Institute of Hematology and Transfusiology of the Federal Medical and Biological Agency, St. Petersburg