

PB1912 *BTK* AND *PLCG2* GENE MUTATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS WITH RESISTANCE TO COVALENT BTK INHIBITOR

Topic: 5. Chronic lymphocytic leukemia and related disorders - Biology & Translational Research

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Background:

Inhibitors of Bruton tyrosine kinase (BTKi) have shown great efficacy in treating chronic lymphocytic leukemia (CLL). However, some patients develop resistance to the drug, leading to treatment failure. Resistance to covalent BTK inhibitors is associated with acquired C481S/F/Y mutations in exon 15 of the *BTK* gene, as well as mutations in *PLCG2* gene. Other *BTK* mutations have been described that could potentially lead to refractoriness. Understanding the mutational landscape of CLL patients with refractory disease on BTKi therapy may help develop new therapeutic strategies.

Aims:

Characterization of *BTK* and *PLCG2* gene mutations in CLL patients with resistance to covalent BTK inhibitors using next generations sequencing.

Methods:

The study included samples from 45 pts with clinical progression on BTK inhibitors therapy. There were 29 men, 16 women, median age 65.5 years (range 47-86), 43 patients received ibrutinib and 2 acalabrutinib. All patients received BTKi for CLL relapse, the median number of previous therapy line was 5 (range 1 – 6). The median duration of BTKi therapy before progression was 34.5 months (range 5,8 – 73 months). Mutations in the *BTK* (11, 15, 16 exons) and *PLCG2* (19, 20, 24 exons) genes and their variant allele frequencies (VAF) were analyzed at time of clinical progression by next generation sequencing (NGS).

Results:

In total 29 (64%) patients had mutations in either *BTK* or *PLCG2* gene. The most common *BTK* c.1442G>C mutation was found in 16 (35.6%) patients, the c.1442G>T mutation was found in 3 (6.7%) patients. In 6 cases (13.4%), two mutations were detected in the same C481 codon of the *BTK* gene. Finally 1 patient had simultaneously 4 mutations in the C481 codon, all with different VAF: c.1442G>C (VAF 32%), c.1442G>T (VAF 17%), c.1442G>A (VAF 7%), c.1441T>C (VAF 1.2%). Other parts of the *BTK* gene were affected by mutations much less frequently. Mutation *BTK* p.L528W:c.1583T>G gene (VAF 3.1%) was detected in 1 patient. One patient had 2 mutations in different domains of the *BTK* gene: p.C481S:c.1442G>C (VAF 33%) and p.T316A:c.946A>G (VAF 0.55 %). In 1 patient, two mutations were found simultaneously in the *BTK* and *PLCG2* genes: p.C481S:c.1442G>C (VAF 25%) and p.L845F:c.2535A>C (VAF 3.4%). Time to progression in patients with mutations was significantly longer compared to patients without mutations (median 38,7 months (9 - 73) versus 25,5 months (5,8 - 57), p = 0,04). Only 1 patient had *BTK* c.1442G>C mutation detected at VAF >1% during the 1st year of treatment; in 21 (72%) patients mutations were detected after 24 months of therapy.

Summary/Conclusion:

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Our study shows that *BTK* and/or *PLCG2* mutations were found in 64.4% of patients with progression of CLL during BTKi therapy, and in 35.6% of patients the cause of resistance has not yet been identified. Most mutations in our sample were detected in the C481 codon of *BTK* gene after 2 years of treatment, suggesting that regular screening with simple PCR tests starting from the second year of treatment is a reasonable approach. NGS may expand data in cases with undetectable mutations. Further research concerning other potential markers of resistance to BTK inhibitors is also required.

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