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ASCIMINIB - A NEW TREATMENT OPTION IN PATIENTS WITH P-LOOP MUTATIONS: CASE REPORT

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INTRODUCTION

Although the most common mutation in chronic myeloid leukemia (CML) is T315I due to limited treatment options, several studies have proven that P-loop mutations are associated with a higher risk of transformation into the blast phase (BP) and unfavorable prognosis.

AIM

We report the case of a patient with a P-loop mutation in the tyrosine kinase inhibitor (TKI) era, where asciminib is one of the therapeutic options.

CASE HISTORY

In May 2020, a 51-year-old male was diagnosed in our institution with chronic phase of CML, with the molecular test showing:

- **b3a2 transcript**
- **Philadelphia chromosome without ACA on the cytogenic examination.**

His prognostic scores were Sokal intermediate risk, Hasford high risk, and EUTOS low risk.

TREATMENT

The patient received dasatinib as first-line TKI treatment and achieved a major molecular response (MMR) after 12 months.

At the 24-month medical visit, the molecular test showed the loss of MMR. The cytogenetic and mutations analyses were negative for T315I mutation, and the patient was switched to nilotinib.

Molecular monitoring showed no MMR achievement at 3, 6, and 9 months.

The cytogenetic examination was negative for additional chromosomal abnormalities, and NGS analysis of BCR-ABL kinase domain (KD) showed E255K/V and V299L mutations.

The patient received asciminib, and the search for an unrelated HLA bone marrow donor is ongoing. After 2 months of asciminib treatment, the transcript level was decreasing (from 59.19% to 23.57%).

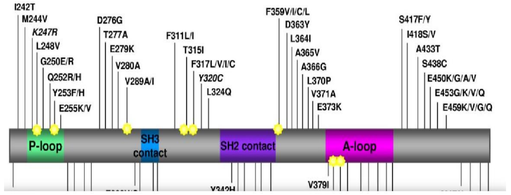


Figure 1. Map of all the amino acid substitutions in the Bcr-Abl KD identified in clinical samples from patients reported to be resistant to imatinib in published papers. Key structural motifs within the KD are indicated. P-loop indicates phosphate binding loop; SH2 contact and SH3 contact, contact regions with SH2 and SH3 domain-containing proteins; and A-loop, activation loop. Star indicates amino acid position reported to be directly involved in imatinib binding via hydrogen bonds or van der Waals interactions.7 K247R and Y320C are in italic because they have been reported to be single nucleotide polymorphisms. Numbering of residues is according to Abl Ia isoform. Data were collated from 27 studies published between 2001 and 2009.1-6,14,16,17,28,35,51-53,61,62,72,82-91 Collapse

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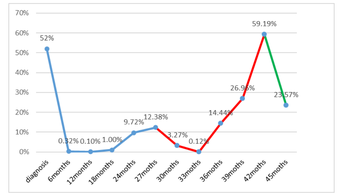


Fig 2. BCR-ABL dynamics

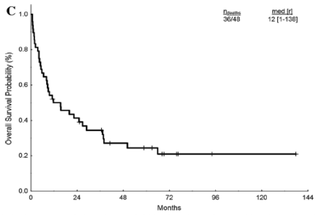


Fig3. Outcome of chronic myeloid leukemia patients with E255K/V BCR–ABL kinase

Naqvi K, Cortes JE, Luthra R, O'Brien S, Wierda W, Borthakur G, et al. Characteristics and outcome of chronic myeloid leukemia patients with E255K/V BCR–ABL kinase domain mutations. Int J Hematol. 2018 Jun 1;107(6):689–95.

CONCLUSIONS

Between 9% and 48% of patients with CML develop mutations during TKI treatment (1)

P-loop mutations gave a very poor prognosis, especially E255K/V, with overall survival being less than 12 months (2).

A small study that included 8 patients with E255K/V mutation achieved MR4 under treatment with asciminib (3).

Unfortunately, in the ASCEMBL study, analysis of mutations was not performed (4).

At the moment, there are no guidelines for treatment in these patients and there are no long-term studies for assessing the effect of asciminib on these mutations.

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