Case Report of NGS Results in the Chronic Myeloid Leukemia Patient with Multiple Resistance to Tyrosine Kinase Inhibitors

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Clinical Case

A female (1959 year of birth) was diagnosed with CML in chronic phase (EUTOS-low risk, Sokal-high risk) according to CBC (leukocytosis, thrombocytosis, shift to blasts); presence of the Ph-chromosome; detecting of *BCR::ABL*(p210,b3a2,b2a2)-43.395% in 12/2018.

Imatinib 600 mg/day since 12/2018 to 03/2019. Complete hematologic response (CHR) was achieved, but the treatment required dose reduction (150-300 mg/day) due to hematological toxicity (neutropenia grade 3). Therapy was discontinued after 3 months due to loss of CHR. No mutations of *BCR::ABL* gene were detected.

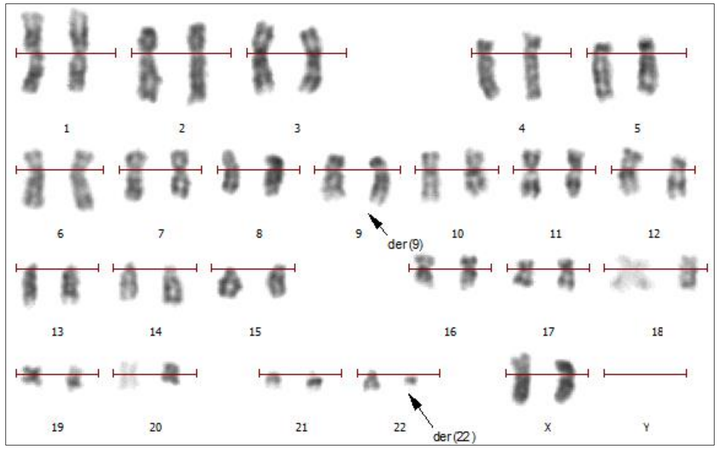
Dasatinib 100 mg/day since 04/2019 to 07/2019. Hematological toxicity (neutropenia, anemia grade 2-3). At 3 months there was a lack of cytogenetic response (100% Ph-positive metaphases), *BCR::ABL*-43.3% by IS.

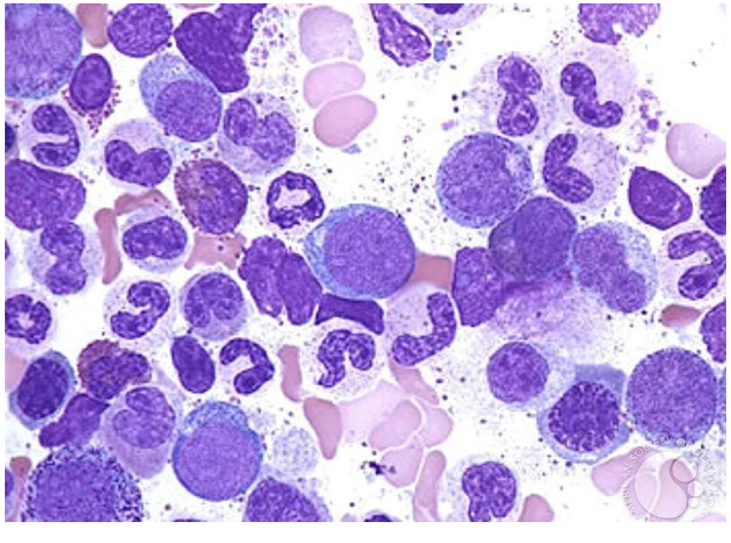
Nilotinib 800 mg/day started on 07/2019 but it was ceased on 08/2019 because of the non-hematologic intolerance (vomiting, nausea, amylase elevation).

Bosutinib 500 mg/day since 09/2019. Treatment was stopped on 12/2019 due to severe neutropenia which persisted for 28 days.

Ponatinib (7.5 mg/day – maximum tolerated dose) since 12/2019 up to date. *BCR::ABL* on 25-Dec-2019 – 31%. Given the multiple resistance to TKIs, next-generation sequencing (NGS) was performed. 32 mutations in 24 genes were detected: 16 were favorable, 9–possible favorable, 7–with unclear significance. Mutations with highest allelic burden were in genes *EZH2, CIITA, CDKN2A, IKZF1, ATM, SETBP1, TET2*.

Ponatinib treatment is still ongoing. Major molecular response (MMR) is not achieved. Neutropenia grade 3-4 persists throughout treatment but therapy is continued due to lack of alternatives.





Results

The discovery of mutated genes by NGS in this patient on multiple lines of TKI-therapy gives the evidence of *non-BCR::ABL* resistance mechanisms.