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PB1790 ABCB1 AS A POTENTIAL BENEFICIAL TARGET OF MIDOSTAURIN IN ACUTE MYELOID LEUKEMIA

Topic: 03. Acute myeloid leukemia - Biology & Translational Research

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Background: In AML, therapeutic outcome of anthracycline-based induction therapy often can be compromised by a resistant phenotype associated with overexpression of ABCB1 transporters. Novel anti-AML agent, midostaurin, was designed to aim at multiple targets including FLT3 mutation. Besides, it was also identified as ABCB1 inhibitor.

Aims: To evaluate ABCB1 efflux activity and expression in primary AML samples in relation to multiple clinical parameters and investigate ABCB1 regulation by microRNA.

Methods: ABCB1 gene expression was absolutely quantified in 28 primary AML samples collected prior to any treatment. Efflux activity was examined using combination of mitoxantrone (ABCB1 substrate) and midostaurin (ABCB1/FLT3 inhibitor). Results were compared in molecular classes defined by CD34 marker, FLT3-ITD and NPM1 mutations, ELN risk classification and (un)achieved complete remission (CR). Enhancement of daunorubicin proapoptotic effect mediated by midostaurin was determined in HL-60 wt and HL-60 overexpressing ABCB1. ABCB1 regulation by microRNAs (miR-9, miR-27a, miR-331) was evaluated by ddPCR and correlated with ABCB1 efflux activity.

Results: High ABCB1 expression was associated with unachieved CR, adverse ELN risk and CD34 positivity. ABCB1 efflux activity was observed in a functional study when mitoxantrone accumulation increased as a direct consequence of midostaurin in CD34+ AML and patients with unachieved CR. ABCB1 efflux activity and expression were found to be linked to miR-9 downregulation

Summary/Conclusion: We propose therapeutic value of midostaurin for drug-resistant patients beyond the FLT3 inhibition based on ABCB1 expression and CD34 positivity. We also propose miR-9 as a predictive ABCB1-related biomarker that could be helpful in identifying ABCB1-resistant AML phenotype.