MIDOSTAURIN INHIBITS ABCB1 AND ABCG2 AND ENHANCES DAUNORUBICIN AND MITOXANTRONE INDUCED APOPTOSIS OF AML CELLS

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Midostaurin is a recently approved FMS-like tyrosine kinase 3 (FLT3) inhibitor for the treatment of patients diagnosed with acute myeloid leukemia (AML), who are positive for FLT3 mutation accountable for a poor prognosis. One of the most common mechanisms responsible for a failure of anticancer therapy is the multidrug resistance (MDR) closely linked to ABC efflux transporters. In this study we aimed to evaluate interaction of midostaurin with ABC transporters using human myeloblastic resistant HL60 cell lines and *ex vivo* isolated peripheral blood monocyte cells (PBMC) from *de novo* diagnosed AML patients.

Using accumulation assays, we found midostaurin to be a potent inhibitor of ABCB1 and ABCG2 in the resistant HL60-ABCB1 and HL60-ABCG2 cells causing higher intracellular levels of mitoxantrone (MIT) or daunorubicin (DNR), the conventional anticancer drugs recognized as substrates of the ABC transporters. Moreover, the annexin V/propidium iodide assays revealed that the resistant cells were more readily driven to apoptosis and necrosis when midostaurine was co-administered with MIT or DNR, surpassing the effect of MIT and DNR alone. No such observations were found in control non-resistant HL60 cells. These data suggest potential of combinations of midostaurin with ABC substrate cytotoxic drugs to trigger cell death in ABC transporter-resistant AML.

Gene expression of ABC transporters was additionally analysed employing qRT-PCR in AML patients' PBMCs (before receiving any treatment). Our results show a noticeable correlation of *ABCB1* and *ABCG2* expression with the effect of midostaurin on accumulation of MIT in PBMC. Therefore, we can assume that the expression of *ABCB1* and *ABCG2* might affect therapeutic outcomes of combination therapy in AML.

To conclude, we show here the potential of midostaurin to inhibit ABCB1 and ABCG2 transporters and contribute to overcoming the pharmacokinetic MDR in AML patients and thereby prevent the pharmacotherapy failure.

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