Abstract

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Student: Adéla Králová

Supervisor: doc. PharmDr. Martina Čečková, Ph.D.

Consultant: Mgr. Simona Suchá

Title of Diploma thesis: Impact of new FLT3 inhibitors on daunorubicin accumulation in ABCB1-expressing leukemic cells

Fms-like tyrosine kinase 3 (FLT3) inhibitors represent a new generation of drugs in the treatment of acute myeloid leukemia (AML). Standard therapeutic regimen of AML is initiated with induction therapy consisting of cytarabine and anthracyclines. The disadvantage of this combination is emerging resistance often caused by the ABCB1-mediated efflux. Therefore, simultaneous inhibition of FLT3 and ABCB1, which is inhibited by FLT3 inhibitors used in clinical practice, appears to be a beneficial approach to therapy. However, their effectiveness is declining hence the effort to develop new FLT3-inhibiting molecules. The aim of our work was to evaluate whether our two promising new FLT3-inhibiting compounds would inhibit ABCB1 as well. Promyelocyte cells overexpressing ABCB1 (HL60-ABCB1) and parent HL60-par were used in this study alongside AML-derived cell lines (MOLM-13, THP-1, Kasumi-1). Employing accumulation studies on HL60-ABCB1, strong inhibitory effect towards ABCB1 was demonstrated for both studied compounds. This work includes characterization of cell lines in terms of *ABCB1* gene expression and protein expression. *ABCB1* expression was confirmed in HL60-ABCB1 both at the mRNA level and protein level (using Western Blotting). Kasumi-1 expressed *ABCB1* very weakly and inhibition of ABCB1 function was not observed. In MOLM-13 and THP-1, *ABCB1* expression was negligible and thus these cells did not represent suitable models for studying ABCB1 function. In conclusion, this study has revealed two novel FLT3 inhibitors as potent inhibitors of ABCB1, which could represent novel compounds with a beneficial combination effect in the treatment of resistant AML.