Abstract

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Student: Jakub Poráč

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

Title of diploma thesis: Effect of CDK and FLT3 inhibitors on activity of ABC efflux transporters *in vitro*, relation to multidrug resistance

P-gp and BCRP are transmembrane proteins that form part of a large family of ABC transporters. These are ATP-driven transporters, which main task is to eliminate exogenous and endogenous substances and their metabolites from cells of both, healthy and tumour tissues. This activity is often associated with the expulsion of administered therapeutics and multiple drug resistance (MDR) in tumour cells. A promising therapy of cancer represents a newer class of drugs target the tyrosine kinase (TK), and cyclin-dependent kinases (CDK), which are cell enzymes responsible for the processes of proliferation, apoptosis and differentiation. Cyclin-dependent kinase inhibitors (CDKI) are used in the treatment of breast cancer, but at the same time they form a new group of drugs with the potential for use in hematological malignancies. In the treatment of AML, a new successful approach is TK inhibitors (TKI), which target the mutated FLT3 receptor, specifically the recently approved drugs midostaurin and gilteritinib. These substances and the new investigative drug FLX925, which acts as both, TKI and CDKI, were the subject of this thesis. Our aim was to study these drugs in terms of inhibition of ABC efflux transporters ABCB1 and ABCG2. The first step was to conduct accumulation studies with selected substrates (daunorubicin and mitoxantrone) on the resistant cell lines HL-60 ABCB1 and HL-60 ABCG2, as well as on the control non-resistant parent cell line HL-60. A clear inhibitory effect on both transporters was found with midostaurin (MID) and gilteritinib (GIL) inhibitors. FLX925 revealed more pronounced inhibition only at the high concentration used (50 μM). In subsequent apoptotic studies, MID and GIL showed a positive potentiated effect over the substrate alone (mitoxantrone). Based on the thesis results, MID and GIL can be suggested as a new generation MDR modulators, and thereby candidates worthy follow up investigations.