Abstract

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Student: Júlia Jurčáková

Supervisor: RNDr. Jakub Hofman PhD.

Title of diploma thesis: The assessment of inhibitory effects of selected targeted anticancer drugs on the activity of ABC drug eflux trasporters.

Lung cancer is the leading cause of death within oncological diseases. Non-small cell lung carcinoma (NSCLC) accounts for about 85% of all lung cancer, and its major subtypes include adenocarcinoma and squamous cell carcinoma. In addition to surgery, radiotherapy and chemotherapy, the use of targeted low-molecular substances, which target tumor cells with higher specificity, has recently been used in treatment. The two main causes of death in cancer patients are the formation of metastases and the development of multidrug resistance (MDR). This may also be caused by overexpression of the efflux transporters. ATP-binding cassette (ABC) transporters are groups of transmembrane pumps that use energy in the form of ATP to transfer a wide range of substrates. In particular, P-glycoprotein (ABCB1), breast cancer-resistance protein (ABCG2) and multidrug resistance-associated protein 1 (ABCC1) are associated with MDR. Inhibition of these transporters increases the amount of cytostatic substrate within the cell and can thus modulate MDR. Our aim was to investigate the inhibitory activity of four selected low molecular weight inhibitors (carfilzomib, encorafenib, enasidenib, sonidegib) against ABC drug transporters on MDCKII cell lines. By comparing accumulation studies with non-cytostatic and cytostatic model substrates, we confirmed the inhibitory effect of sonidegib and enasidenib. Flow-cytometric analysis also showed the inhibition of sonidegib in primary cell culture, which was obtained from biopsies of non-small cell lung cancer tumors. The results of this work may serve as an important source of information in the further study of pharmacokinetic drug interactions and MDR modulation.