Abstract

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Student: Barbora Žofajová

Supervisor: doc. RNDr. Jakub Hofman, Ph.D.

Title of diploma thesis: Expression of ABC transporters in non-small cell lung carcinoma cell cultures: effect of selected targeted drugs

ABC transporters form a special family of transmembrane proteins, their function is the active efflux of substrates into the extracellular environment. These transporters are expressed in normal tissues and tumor cells. Thus, they influence drug pharmacokinetics and play a role in the development of multidrug resistance (MDR). Tyrosine kinases have essential functions ranging from proliferation to differentiation and cell death, their mutation can cause carcinogenesis. Finding, exploring, and inhibiting the functions of these targets is a promising strategy to treat cancer.

This work aimed to determine whether the selected drugs are involved in pharmacokinetic interactions that are based on inductions of ABC efflux transporter genes and whether they have the potential to affect MDR phenotype of tumor cells. The drugs, which we studied, were three targeted anticancer drugs (capmatinib, pralsetinib, and tazemetostat) and two well-known chemotherapeutic drugs (pemetrexed and methotrexate). First, we investigated the antiproliferative effects of the drugs. Subsequently, we used obtained results for the design of induction studies, in which we studied the effect of tested drugs on the expression of ABC transporters at the mRNA level, using two intestine model cell lines (LS174T, Caco-2) and two model non-small cell lung cancer cell lines (HCC-827, NCI-H1975). None of the drugs exhibited significant induction properties, which suggests their minimal potential to become perpetrators of pharmacokinetic drug interactions or the drivers of pharmacokinetic resistance. In conclusion, we can state that our results provide important pieces of information regarding the induction profile of tested drugs, which can be used within the optimalization of therapy of oncological patients for the maximalization of its safety and efficacy.