Abstract

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Title of diploma thesis: Study on interactions of PARP inhibitors with ABC drug efflux transporters.

ATP-binding cassette (ABC) transporters are integral membrane proteins that use the energy obtained from ATP to carry transport of numerous endogenous substrances out of the cells, but attention is drawn primarily to the fact that they transfer also xenobiotics. Their overexpression in tumor tissue contributes to multidrug resistance (MDR), which in most cases leads to therapy failure. Poly(ADP-ribose)polymerase inhibitors (PARPi) represent a promising therapeutic approach in the treatment of cancers that exhibit defects in homologous recombination (HR). This work focuses on four selected PARPi (olaparib, rucaparib, niraparib, veliparib) and their interaction potential towards ABC drug efflux transporters (ABCB, ABCC1, ABCG2). In our work, we worked with MDCKII cells (parent, transduced by the transporters of interest) and utilized the principle of accumulation studies based on the measurement of fluorescence intensity of specific model substrates (hoechst33342, calcein AM, daunorubicin, mitoxantrone). We used established inhibitors of studied transporters as a positive inhibitory control. Slight inhibitory potential was found for olaparib (ABCG2) and niraparib (ABCB1). There was no significant inhibition of examined ABC efflux transporters exhibited by rucaparib and veliparib. In conclusion, we can sum up that we were able to expand our knowledge of the pharmacokinetic profile of PARPi. Our work can serve as an important source of information that, once verified on multiple models, could be useful for the safe clinical use of these drugs.