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Title of diploma thesis: Study of the effect of ABC drug transporters' overexpression on the antiproliferative capacities of selected conventional cytostatics

Overexpression of ABC drug transporters is one of the mechanisms of multiple drug resistance development, which results in therapy failure in cancer. ABC transporters such as ABCB1, ABCG2 and ABCC1 have a wide range of substrates, including several conventional cytostatics.

This study aimed to examine the influence of overexpression of the mentioned transporters on the antiproliferation effects of docetaxel, etoposide, paclitaxel, methotrexate, pemetrexed, topotecan and vinblastin. The results were obtained with the MTT assay in which the MDCKII and A431 cell lines with/without overexpression of mentioned transporters were used. A decrease of cytotoxicity in the presence of at least one of the transporters was observed in five of seven tested cytostatics. Only topotecan has been proven to be the victim of overexpression of all of the tested transporters.

To prove the applicability of the obtained results, topotecan was used in the follow-up combination study. Within this study, I have tested capmatinib, pralsetinib and tazemetostat as potential inhibitors of ABCG2 transporter. According to the MTT assay results, all of these drugs had shown a potential to be transporter modulators in combination with topotecan.

Despite several years of research, we still do not have ABC transporter inhibitors that would be successful in clinical conditions. Therefore, it is important to constantly look for new modulators as well as to describe molecules that are victims of the MDR. This work may be beneficial for further studies dealing with the issue of overexpression of ABC transporters and its impact on chemotherapy failure. In addition, it brings new knowledge about capmatinib, pralsetinib and tazemetostat as potential ABCG2 modulators.