Abstract

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Title of diploma thesis: Study on impact of selected tyrosine kinase inhibitors on multidrug resistance mediated by ABC drug efflux transporters

Tyrosine kinases are an important class of enzymes controlling cell proliferation, carcinogenesis, apoptosis and cell differentiation. Deregulation of these enzymes can transform normal cell into a cancerous one. Blocking their function by tyrosine kinase inhibitors (TKi) is considered a promising treatment for various types of cancer. ATP-binding cassette (ABC) transporters form a family of transmembrane proteins that can transport a wide variety of substrates across biological membranes via ATP-dependent drug efflux pumps. They modulate drug pharmacokinetics, but on the other hand, lead to therapy failure due to overexpression in cancer cells. In our previous study, we evaluated inhibition properties of two selected TKi (alectinib, brivanib) in MDCKII cell lines (parent one and those transduced with human ABCB1, ABCC1 and ABCG2). Alectinib significantly inhibited ABCB1, ABCG2 but not ABCC1 transporter. Brivanib showed triple inhibition of all studied transporters. In the present work, we evaluated combinations of alectinib and brivanib with cytostatic substrates of ABC transporters, daunorubicin and mitoxantrone and their potential ability to overcome multidrug resistance (MDR) to these cytostatic agents. We showed that simultaneous administration of the TKi and the cytotoxic substrate of ABC transporter may lead to increased intracellular accumulation of the substrate and to pronounced synergistic anticancer effect. Thereafter, we investigated the effect of these novel anticancer drugs on expression of ABC transporters at mRNA level using LS174T, A549, Caco-2 and NCI-H1299 cells. In conclusion, our results could serve as a valuable foundation for follow-up *in vivo* studies and potentionally bring an effective therapy for many oncology patients.