ABSTRACT

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Title of diploma thesis: The effect of tyrosine kinase inhibitor tirabrutinib on anthracycline resistance in a cancer cell line

Malignancies represent a broad spectrum of heterogeneous diseases caused by genetic and epigenetic alterations that negatively affect various human tissues, contributing to the development of malignancy. Chemotherapy is considered one of the main pillars in the treatment of malignant diseases. Anthracycline chemotherapeutics are widely used drugs in these indications. However, adverse effects resulting from their mechanism of action are a major obstacle. The role in the development of cardiotoxicity, as one of the adverse effects of therapy, is played by carbonyl reducing enzymes that produce toxic reduced metabolites by conferring metabolic reduction of anthracyclines. At the same time, these metabolites show significantly lower cytotoxic activity, thus contributing to the formation and further development of resistance, another severe obstacle in clinical practice.

This thesis aimed to investigate the inhibitory effect of a specific tyrosine kinase inhibitor tirabrutinib at the cellular level. The HCT116 cancer cell line was transiently transfected with a plasmid encoding the enzyme AKR1C3. Results demonstrated that the 10 and 50 μM concetrations of tirabrutinib reduced the activity of AKR1C3 by 41,17 % and 76,56 % (IC_{50} 12,01 μM), respectively. In addition, the study focused on the combination of daunorubicin with tirabrutinib in the AKR1C3 overexpressing cancer cell line HCT116. It follows, that combining daunorubicin with tirabrutinib reduces the viability of HCT116 cancer cells more than daunorubicin alone. This fact suggests that the inhibitory activity of tirabrutinib can be used to resensitize resistant cancer cells to daunorubicin, increasing its therapeutic effect while reducing the production of toxic reduced metabolites.