Abstract

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Title of diploma thesis: The effect of zanubrutinib on tumor cell resistance to daunorubicin due to carbonyl reducing enzymes

Anthracycline antibiotics (ANT) are considered the first-line medication for oncologic diseases, including acute myeloid leukemia. Daunorubicin (DAUN) with a carbonyl group in position 13 is often used in chemotherapeutic treatments. Nicotinamidadenindinucleotid-phosphate dependent carbonyl reducing enzymes (CRE) create its hydroxyl metabolite daunorubicinol (DAUN-ol), which demonstrates higher toxicity on myocardial tissue and lower cytotoxicity on cancer cells, which acquire tolerance towards its effects. Overexpression of enzymes catalyzing the conversion of effective antineoplastic DAUN causes the gradual development of resistance to administered ANT. For this reason, the new pharmacotherapeutic options for preventing this process are being searched for to maintain the drug in the target cell as long as possible. One option is to use inhibitors, which lower enzymatic activity CRE and prevent unfavorable DAUN metabolism on cardiotoxic and ineffective DAUN-ol. This diploma thesis aimed to study the inhibition of zanubrutinib (ZANIB) on the activity of the enzymes from aldo-keto reductase (AKR) and short-chain dehydrogenase/reductase superfamilies (SDR). Selected enzymes were incubated with substrate DAUN and inhibitor ZANIB. The amount of created product DAUN-ol, recalculated on specific enzyme activity, was measured by ultra-high performance liquid chromatography. AKR1C3 was the most inhibited enzyme from all tested CREs, with inhibition potentials of 79.1 % (ZANIB 10 μM) and 88.5 % (ZANIB 50 μM), and was the only enzyme used for the following parts of the experimental work. The value of inhibitory concentration IC50 was 4.90 ± 2.10 μM, and the value of kinetic constant Ki was 4.56 ± 0.40 μM. Then were defined the type of inhibition and the type of bonding with the enzyme. Based on the measured results, ZANIB is a non-competitive inhibitor that binds non-reversibly with AKR1C3. We can conclude from the study that using ZANIB in oncological therapy could lower adverse effects and improve the therapeutical effect of ANT administered at the same time