Abstract

Tyrosine kinase inhibitors (TKI) are small organic molecules designed for the targeted cancer therapy. They perform the inhibition of activated receptor tyrosine kinases in tumor cells, that defeats tumor growth, proliferation, metastasis and angiogenesis in tumor tissue. Two TKI, lenvatinib and vandetanib, are used in thyroid cancer treatment. This thesis investigates the ways leading to enhancement of efficiency of these anticancer drugs for therapy.

One of the studied anticancer drug – lenvatinib – was investigated to be prepared in a nanoform. Nanoparticles were based on protein apoferritin as well as on lipids.

Theoretical model of lenvatinib interaction with an apoferritin cavity, as well as the model of its encapsulation obtained by computer modeling indicated that lenvatinib seems not to be suitable for preparation of apoferritin nanoparticles. Since lenvatinib occurs in its neutral form during preparation of nanoparticles, it does not interact with nanoparticle. The unsuccessful experimental preparation of lenvatinib-loaded apoferritin nanoparticles confirmed that lenvatinib is not suitable for its preparation. However, the theoretical model can serve for screening of other potentially suitable drugs before the experimental nanoparticle preparation.

Since the experimental preparation of apoferritin nanoparticles was not successful, we used liposomes as lenvatinib nanocarriers in further experiments. The amount of prepared nanoparticles is however low, therefore not relevant for cancer therapy.

The second anticancer drug, which we focused on, was vandetanib. It was found that the metabolism of vandetanib influences the efficiency to vandetanib during therapy. Vantedanib is oxidized into *N*-desmethylvandetanib, by the reaction that is catalyzed by human CYP1A1, 2D6 and 3A4. The most effective oxidation is carried out by CYP3A4. Moreover, the presence of cytochrome b_5 significantly increases the yield of reaction. In order to explain this effective oxidation, we investigated the enzyme kinetics of vandetanib oxidation by mentioned CYPs.

The study of enzyme kinetics of vandetanib oxidation by human CYP1A1 and 2D6 showed that only one molecule of vandetanib binds into their active sites. On the contrary, sigmoidal enzyme kinetics of vandetanib oxidation by CYP3A4 showed that two molecules of vandetanib can be bound into the active site. Experimental results of enzyme kinetics were in accordance with the results found by molecular “docking”. As a result, binding of two molecules of substrate vandetanib into the active site of CYP3A4 allows

more effective oxidation of vandetanib by this enzyme in contrast to the oxidation catalyzed by CYP1A1 and 2D6.

Key words: tyrosine kinase inhibitors, nanoparticles, lenvatinib, vandetanib, cytochrome P450