Abstract

Lenvatinib, commercially marketed as Lenvima®, is an oral drug approved for the treatment of thyroid cancer, hepatocellular carcinoma and renal cell carcinoma that acts as a tyrosine kinase inhibitor. In vitro and in vivo studies have shown that lenvatinib is in the human body metabolised in liver and kidney by the cytochrome P450 enzyme system and aldehyde oxidase.

Therefore, the aim of this bachelor thesis was to determine the effect of lenvatinib on the activity of individual isoforms of human cytochrome P450. Among the isoforms studied, those that ensure the metabolism of majority of foreign substances in the human body were selected. Measurements were performed in vitro using recombinant CYPs expressed in Supersomes^{TM} and using marker reactions that are provided by individual cytochrome P450 isoforms.

The activity of the enzyme in the reaction mixtures containing lenvatinib was compared with the activity of the enzyme in the reaction mixtures where only the solvent DMSO was added instead of lenvatinib. The concentration of lenvatinib corresponded to the concentration of the given substrate or was 10 times higher. Based on these measurements, the percentage activity of cytochrome P450 isoforms 1A1, 1A2, 1B1, 2B6, 2C8, 2C9, 2E1 and 3A4 in the presence of lenvatinib was calculated.

A decrease in activity of CYP1B1, CYP1A1 and CYP3A4 isoforms was observed. The most significant inhibition occurred in the CYP1B1 isoform, where the IC_{50} value was subsequently determined to be 13,1 μM. An inhibitory effect was also found for CYP2C8 and CYP2C9 isoforms, suggesting that lenvatinib acts as a mild inhibitor of the CYP2C subfamily.

The results showed that lenvatinib did not significantly alter cytochrome P450 activity and therefore should not play a significant role in drug-drug interactions that may lead to adverse events or treatment failure.

Key words: lenvatinib, cytochrome P450, enzyme activity, inhibition