Abstract

This bachelor thesis is aimed to study the mechanisms of action of anticancer drugs, their side effects, their resistance and pharmacokinetics. Anticancer alkaloid ellipticine was chosen as a model for this work. Bachelor thesis describes the metabolism of this substance in organisms and its potential to induce of drug metabolizing enzymes.

An antineoplastic alkaloid ellipticine is a prodrug, whose mode of action is based mainly on DNA intercalation, inhibition of topoisomerasa II, and formation of covalent DNA adducts mediated by cytochromes P450 and/or peroxidases in target tissues. A variety cytochromes P450 oxidize ellipticine forming up to five metabolites (7-hydroxyellipticine, 9-hydroxyellipticine, 12-hydroxyellipticine, 13-hydroxyellipticine and ellipticine N^2- oxide). 7-hydroxy- and 9-hydroxyellipticine metabolites are considered to be mainly the detoxication products of ellipticine, while 12-hydroxyellipticine, 13-hydroxyellipticine and ellipticine N^2-oxide are considered to be mainly the activation products of ellipticine. The major ellipticine-derived DNA adducts are generated from these activation metabolites. These adducts were found in cancer cells in culture, such as human breast adenocarcinoma MCF-7 cells, neuroblastoma IMR-32, UKF-NB-3, and UKF-NB-4 cells and glioblastoma U87MG cells *in vitvo*. Both mainly DNA adducts were also detected in DNA of rat breast adenocarcinoma *in vivo.* The reactive carbenium ionts, ellipticine-12-ylium and ellipticine-13-ylium, are generated by spontaneous cleavage of 12-hydroxyellipticine and 13-hydroxyellipticine, without participation of cytochromes P450. Deoxyguanisine was identified as target base to which reactive carbenium ionts of ellipticine metabolites generated by cytochromes P450 are bound. Peroxidases oxidize ellipticine to species binding to DNA. The ellipticine oxidation products formed by peroxidases are the ellipticine dimer and ellipticine N^2-oxide. This drug was found to induce CYP1A, 1B1 and 3A4 in cancer cell line and/or *in vivo* in rats exposed to ellipticine. Because of the high efficiency of ellipticine and its derivatives against various types of cancer, this compound is suitable to prepare its derivatives useful for tumor targeting.

Key words:

Anticancer drugs, biotransformation of drugs, antitumor alkaliod ellipticine, cytochrome P450, peroxidase, DNA adducts in target tumor.