ABSTRACT

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Title of Doctoral Thesis **POSSIBILITIES TO INCREASE THE EFFECTIVENESS OF SELECTED CYTOSTATICS**

Cancer belongs among the most serious diseases and one of the most common causes of death in civilized countries. Many cancers can be cured by surgery, radiotherapy or chemotherapy, especially if they are detected early. The efficacy of anticancer treatments is frequently insufficient; the use of higher doses is limited by the development of systemic or organ toxicity. Recently, new strategies how to improve efficacy of cytostatics in cancer cells and decrease their toxicity in normal healthy cells have been intensively investigated.

The aim of present thesis was to search and test the new possibilities, how to increase effectiveness of anticancer drugs. To achieve our goals, in vitro experiments (various cell culture, subcellular fractions of homogenate from cells, rats and mice) and in vivo experiments (tumor bearing mice) were performed.

First tested approach was based on the inhibition of doxorubicin deactivation (DOX), which belongs among the most important antineoplastic drugs used in cancer therapy. DOX is metabolized to less cytostatically active and more cardiotoxic metabolite doxorubicinol (DOXOL). The inhibitory effect of isoquinoline derivative oracin (ORC) on DOX reduction in tumorous and non-tumorous breast cancer was studied. In vitro, ORC inhibited DOX reduction and increased the antiproliferative effect of DOX in MCF7 breast cancer cells. Moreover, ORC significantly decreases DOX toxicity in non-cancerous MCF10A breast cells and in hepatocytes. In vivo, ORC was able to reduce DOXOL formation but was not able to improve DOX efficacy in EST-bearing (Ehrlich solid tumor) mice.

Tumor-target therapy based on specific molecule for selective transport of drugs into cancer cells was used to improve the effect of paclitaxel (PTX), other potent chemotherapeutic drug. PTX was conjugated with gonadotropin-releasing hormone (GnRH), whose receptor is mostly expressed in breast and ovary carcinoma. This conjugate was found to be more effective than PTX alone in decrease of cell proliferation in MCF7 human breast cancer cells.

Further studied approach comprised the tests of antiproliferative effect of drugs, which are approved for administration in other indications.Our study was focused on benzimidazole anthelmintics, flubendazole (FLU) and albendazole (ABZ), which were recently found to be cytostatically active in several types of tumors. In our study, significant antiproliferative effect of FLU and ABZ was observed in intestinal cancer cells. In addition, ABZ and FLU potentiated efficacy of PTX in these cancer cells.

The search of new drugs with cytostatic effects, e.g. from natural extracts represents another possible approach to increase the effectiveness of anticancer treatment. In our experiments, different extracts and oils from tropical tree Myrica rubra were tested. The oil pressed from the leaves had significant antiproliferative effect on intestinal tumor cell lines Caco2 and HCT8. Identification of active substances and possible mechanisms of action is now intensively studied.

The obtained results extend the knowledge of possible ways how to increase the effectiveness of anticancer therapy and at least partially helped to understand other relevant approaches in this area.