„Mechanism regulating vitamin D analog cooperation with cytostatics and tyrosine kinase inhibitors in non-small cell lung cancer model”

Summary

The aim of this dissertation was the evaluation of the mechanisms of the cooperation of vitamin D compounds with tyrosine kinase inhibitors: imatinib and sunitinib together with cytostatics: cisplatin and docetaxel in non-small cell lung cancer A549 model. The cytotoxic effect of tested compounds in different combination was evaluated on A549 lung cancer cells and HLMEC endothelial cells, as well as the influence of such combination on cell cycle and cell death was tested. Next, the changes in expression of proteins engaged in cell cycle regulation, angiogenesis and the action of vitamin D was analysed. Moreover, the influence of vitamin D compounds on anticancer activity of imatinib and sunitinib, the second agent also in combination with docetaxel, was studied in A549 lung cancer model *in vivo*.

Tested vitamin D analogs: PRI-2191 and PRI-2205 augumented anticancer activity of imatinib in A549 lung cancer *in vivo*. Sunitinib together with docetaxel and PRI-2191 showed stronger anticancer activity in A549 lung cancer model *in vivo* compared to double combinations and compounds given alone. Studies aiming at evaluating cytotoxicity of combinations of tested agents showed that imatinib and sunitinib together with cisplatin or docetaxel revealed stronger antiproliferative activity *in vitro* on A549 lung cancer cells and HLMEC endothelial cells. PRI-2191 and calcitriol augumented the cytotoxic effect only in case of endothelial cells. Incubation of A549 cells with combination of imatinib and sunitinib with cisplatin and docetaxel increased the cell death, but only after treatment with imatinib alone or in combination with cytostatics the activity of caspase 3 was increased, whilst treatment with sunitinib lowered the activity of that protease. Vitamin D compounds augumented caspase 3 activity in endothelial cells, but decreased in A549 lung cancer cells. Cytostatics: cisplatin and docetaxel given alone or in combination with imatinib, sunitinib and with PRI-2191 or calcitriol induced p53 and p21 protein expression in A549 cells. Among tested agents, sunitinib and cisplatin down-regulated the secretion of VEGF-A from A549 lung cancer cells. Decrease in VEGF-A level after incubation with cisplatin correalted with higher p53 protein expression, whilst no such correlation was observed after treatment of A549 cells with sunitinib.

Tested vitamin D compounds improve anticancer activity of tyrosine kinase inhibitors imatinib and sunitinib in non-small cell lung cancer A549 model *in vivo*. Observed anticancer activity may be the result of the influence of tested agents on process of tumor angiogenesis, *e.g.* down-regulation of VEGF-A expression, also the induction of cell death inside the tumor.