SUMMARY

The main aim of this work was the evaluation of the influence of vitamin D_3 analogs: PRI-2191 (tacalcitol) and PRI-2205 (5,6-trans isomer of calcipotriol) on the anticancer activity of selected chemotherapeutics (cyclophosphamide, gemcitabine and anastrozole) in mammary gland cancer models *in vitro* and *in vivo*. The best results were obtained both: *in vitro* and *in vivo* for vitamin D_3 analogs in combined treatment with anastrozole. The T47D human mammary gland cancer cell line revealed the highest sensitivity towards both analogs and calcitriol of all cancer cell lines used in these work.

The *in vitro* studies showed that PRI-2191 and PRI-2205 enhance the antiproliferative activity of gemcitabine and anastrozole against all used human cancer cell lines. The influence on cell cycle and the expression of estrogen receptors was evaluated after treatment with vitamin D_3 analogs used alone or in combined treatment with anastrozole. A decreased expression of ERα receptor was shown after treatment with both analogs used alone or when combined with anastrozole. The analog PRI-2191 and calcitriol revealed also the ability to inhibit aromatase activity in an enzymatic assay. It was observed that both analogs and calcitriol can regulate the transcription of genes like aromatase, estrogen receptors ERα and ERβ, hydroxysteroid (17-beta) dehydrogenase, estrogen sulfotransferase and FSH receptor in human mammary gland cancer cells. The best results in decreasing the mRNA for ERα were observed after treatment with calcitriol and PRI-2191 alone or PRI-2205 combined with anastrozole. Similar effects were observed for ERβ, aromatase and estrogen sulfotransferase genes expression.

It was shown, that PRI-2191 and PRI-2205 enhance the antitumor activity of anastrozole *in vivo*. The best effect of combined treatment was observed in human MCF-7 mammary gland cancer xenograft model. Both analogs used alone revealed high anticancer activity. The activity of anastrozole was significantly enhanced when combined with PRI-2191 or PRI-2205. Moreover, PRI-2191 combined with anastrozole decreased significantly the estradiol and calcium levels in serum from mice. In tumor tissue harvested from mice bearing MCF-7 tumors a decrease of ERα was shown after treatment with RPI-2191, PRI-2205 and anastrozole used alone or after combined treatment with PRI-2191 and anastrozole. An increased level of VDR and CYP27B1 was observwed in tumors from mice treated with PRI-2191.

Summarizing, both tested vitamin D_3 analogs are good candidates for combined treatment with aromatase inhibitors which are used in therapy of patients with breast cancer.