Summary

Despite the increasing advances in medicine, cancer remains one of the leading causes of death. With regard to many cancers, including prostate cancer, we still observe that classical therapeutic options do not allow for the complete recovery of the patients that are already affected by an advanced stage of disease with multiple metastases present. Nowadays, new therapeutic methods are being sought based both on a combination of existing therapies in order to obtain synergism as well as the sensitization of prostate cancer cells to currently already available therapy. One of the proposed strategies constitutes the combination of classical therapy, which includes chemotherapy, radiotherapy with other agents of moderate toxicity. The choice of an additional factor aimed at enhancing the effectiveness of classical therapy must be motivated by the knowledge of the tumour biology and the changes that occur within the tumour cell. The changes observed in most cancers include changes in the activity of the energy-harvesting pathways. This effect is referred to as the Warburg effect and it is based on the activation of glycolysis despite the unhindered access to oxygen.

The aim of the research was to assess the possibility of sensitization of prostate cancer cells to classical cytostatics and X-rays with the use of model compounds that act by disturbing the function of mitochondria. Furthermore, the research attempted to define the criteria for the classification of metabolic phenotypes of the studied cell lines and an attempt was made to relate these phenotypes to the expected synergy effects, based on the consumption of exogenous glucose, lactate synthesis and a decrease in ATP concentration due to the use of 2,4-DNP.

The research was performed with the use of three prostate cancer cell lines: PC-3, DU-145 and LNCaP. There have been used three model compounds that disrupt the proper functioning of mitochondria through different mechanisms of action: 2,4-dinitrophenol (2,4-DNP), ethanol and potassium cyanide. For further studies on the effects of the combined use of X-rays and classic cytostatics, only 2,4-DNP at a concentration of 100 μM was selected. The evaluation of the metabolic phenotype of tested cell lines was assessed by the measurement of glucose concentration and lactate concentration in the cell culture medium during the 72-hour incubation of cells. In addition, the concentration of mitochondria in tested cells was assessed using the fluorescent staining as well as the inhibition of ATP synthesis by 2,4-DNP was assessed. The X-ray dose for the further research on the combined effect with 2,4-DNP was selected on the basis of changes in cell morphology and cell cycle analysis, while the concentration values of fifteen classical cytostatics were selected on the basis of the MTT assay. The assessment of the combined effect of the use of X-rays at a dose of 10 Gy with 2.4-DNP at a concentration of 100 μM was carried out on the basis of the analysis of cell morphology and the cell cycle as well as using the MTT and CVS assays. The evaluation of the effect of the combined use of classical cytostatics with 2,4-DNP was performed with the MTT assay. Thereafter, a cell cycle analysis was performed to confirm the possible synergistic effect observed in the MTT assay.

As a result of the research, the following conclusions were drawn: (1) The cytotoxic activity of 2,4-DNP in combination with X-rays was synergistic only in relation to the LNCaP line. (2) Also, only in the case of the LNCaP line, synergism of the cytotoxic effect of anticancer drugs with 2,4-DNP was observed. Such synergy was demonstrated in the case of combination of 2,4-DNP with vinca alkaloids (vincristine, vinorelbine), anthracyclines (doxorubicin, epirubicin), cisplatin and etoposide. (3) Based on the analysis of changes in the concentrations of exogenous glucose, lactate as well as the observation of the decrease in ATP concentration due to 2,4-DNP, the following criteria of the metabolic phenotype can be defined: the efficiency of lactate synthesis, the origin of lactate from sources other than glucose, the degree of exogenous glucose utilization and the potential/dependence on oxidative phosphorylation. (4) Among the above-mentioned criteria, the LNCaP cell line, in which synergistic effects of X-rays and cytostatics were observed, is distinguished by an extremely low level of glucose utilization and a high oxidative phosphorylation potential/dependence. Further research may elucidate whether synergy is dependent on such a pattern of metabolic phenotype.