Summary

The main purpose of this study was to assess the possibility of sensitizing cancer cells to classic therapeutic agents - cytostatics and X-rays through the inhibition of glucose catabolism pathways. An additional aspect of this work was to evaluate the sensitivity of tumor cells to glucose catabolism inhibitors in combination with Elesclomol, a drug disturbing the function of mitochondria, paired with CuCl2. In addition, the aim of the study was to try to use cyanides as a tool compound to assess the metabolic phenotype, which in the future may enable the search for molecular mechanisms responsible for sensivity to glucose catabolism inhibitors dependent on the respiratory phenotype.

The choice of the dose ranges of glucose catabolism inhibitors was based on the literature, and then verified in preliminary studies on cells with particularly high sensitivity to inhibition of glucose catabolism, such as erythrocytes and cardiomyocytes. Then without exceeding the established maximum doses from the preliminary studies(25, 50 and 100 μM), screening tests were carried out for the sensitivity of tumor cells to glucose catabolism inhibitors, such as: 3-bromopyruvate, 2-deoxyglucose, sodium dichloroacetate, and dehydroepiandrosterone. Cytostatics in the cell culture medium mixture, alone or in combination with tested inhibitors, were used at the following concentrations: 0.5 and 2.5 μM for doxorubicin, 10 and 20 μM for cisplatin, 5-fluorouracil - 20 and 100 μM, vincristine - 10 and 50 μM, bortezomib - 10 and 50nM, which were selected based on the maximum concentrations of individual cytostatics in the blood of patients undergoing chemotherapy described in the literature. X-ray doses and incubation time were optimized in preliminary studies. After 24 hours of incubation with glycolysis inhibitors, the cells were exposed to 2, 8, and 10Gy doses of radiation and incubation was continued for another 72 hours. Elesclomol in a cell culture medium mixture containing glucose catabolism inhibitors was used at concentrations of 0.2μM Elesclomol +4 μM CuCl2 and 0.1μM Elesclomol + 2 μM CuCl2. Evaluation of cytotoxicity in individual groups of subjects was carried out using the MTT test, which is the standard test used to assess cell viability. Significant changes in the MTT test were verified by microscopic observation. In addition, for maximum doses of radiation (10Gy) used with inhibitors of glucose catabolism, the changes of the cell population in the cell cycle phases were determined.

Based on the obtained results, the following conclusions were drown:

- There was no synergistic effect of cytotoxic activity for the strongest inhibitors of glucose catabolism, such as: 3BP and DHEA with anti-cancer drugs;
- There was no synergistic effect of cytotoxic activity for the strongest inhibitors of glucose catabolism, such as: 3BP and DHEA with X-ray;

- There was no synergy of cytotoxic activity between glucose catabolism inhibitors and Elesclomol/Cu;
- It can even be concluded that glucose catabolism inhibitors reduce cytotoxicity of Elesclomol/Cu;
- The use of only cyanides as a tool compound substance to assess the metabolic phenotype of tumor cells has some limitations, and therefore additional tests should be used at the same time;
- It was shown that the lower concentration of doxorubicin in melanoma cell lines abolishes the action of 3BP - understanding the mechanism of this phenomenon may be an interesting direction for further studies.