Summary

Ovarian carcinoma is a heterogeneous group of diseases usually of epithelial origin. The vast majority of diagnosed cases are high-grade serous carcinomas, which account for over 80% of all cases. Ovarian carcinoma is one of the most common causes of death in women from gynecological malignancies. The main cause of high mortality is diagnosis of the disease in late stages due to the long-term asymptomatic course. The second important cause is the development of multidrug resistance to the administered treatment, which is in the case of ovarian carcinoma patients still mainly based on a combination of paclitaxel and platinum derivatives - cisplatin or carboplatin. These are some of the reasons that motivate scientists to search for new biomarkers, which could help detect the disease in early stages, or monitor the success of treatment, and predict the development of resistance. Molecular characterization of cancer in general may also reveal new therapeutic targets. The development of resistance to already existing drugs stimulates the direction of scientists to prepare new drugs that would be especially effective against already resistant tumors.

The main aim of the presented theses was to expand information on the molecular profile of ovarian carcinoma, to reveal prognostic and predictive molecular biomarkers of ovarian carcinoma and to identify genes that play a role in the development of multidrug resistance. Another important aim of the work was to study the efficacy of new taxane derivatives - the Stony Brook taxanes, potentially effective in the therapy of resistant tumors.

During the study of the molecular profile of ovarian carcinoma, a connection was found between the expression levels of membrane ABC transporters, players in the development of resistance, and specific sensitivity to administered chemotherapy. Specifically, chemotherapy-sensitive status and longer time to progression were associated with reduced expression of ABC transporters – *ABCC4, ABCC10, ABCD3, ABCE1, ABCF1, ACBF2,* and *ABCF3*. In contrast, chemotherapy-resistant status was associated with increased expression of *ABCB1, ABCG2* and decreased expression of *ABCB11*. Patients with this expression profile progressed faster.

A comprehensive analysis of the molecular profile (expression, methylation profile, and genetic variability) of the DNA repair system showed interesting candidates for further studies in the development of resistance to taxanes and platinum derivatives. The analysis revealed the interaction of *XPC-PRKDC-FAAP20* and *BRCA1-RAD9A-RBBP8* genes in connection with response to chemotherapy. A higher methylation level of the *RAD50* gene was also observed in patients with chemotherapy-resistant status. The presence of somatic mutations in the *XPC* and *PRKDC* genes significantly worsened the overall survival of patients. Among other things,

higher expression of the *DUT* gene was associated with the presence of peritoneal metastases. The high-grade serous subtype was associated with a higher number of mutations in the *TP53* gene, compared to other subtypes of ovarian carcinoma.

The second part of the work, focused on new experimental drugs, was an analysis of the efficacy of the new taxane derivatives, both the second (SB-T-1214 and SB-T-1216) and especially the third generation (SB-T-121402, SB-T-121605, SB -T-121606) was found to be more effective than paclitaxel in an *in vitro* model of ovarian carcinoma. Compared to paclitaxel, the new taxanes induced cell arrest in the G2/M phase of the cell cycle almost more than 50 times, and their intracellular concentration was also significantly higher compared to paclitaxel. The most stable effect was observed with the taxanes SB-T-121605 and SB-T-121606. The efficacy of SB-T-121605 and SB-T-161605 was also observed in an *in vivo* model of resistant ovarian carcinoma, where their application led to a slowdown of tumor growth, and at a higher concentration of SB-T-121606 (3 mg/kg) in combination with paclitaxel also in reduction of the tumor size.

Of the other candidate molecules, CPS1 (carbamoyl-phosphate synthase 1), a mitochondrial enzyme involved in the urea cycle, turned out to be the most promising candidate for further detailed studies. CPS1 expression is often increased in tumor tissue and especially in the resistant tumors. In our study, high expression of *CPS1* in ovarian carcinoma tumor tissue samples was significantly associated with a shorter time to progression, so it could be potentially used as a prognostic biomarker. In addition, CPS1 expression was affected by taxane administration. In our *in vitro* and *in vivo* resistant ovarian carcinoma models, there was a significant reduction in CPS1 expression after administration of the new third generation taxane derivatives – SB-T-121605 and SB-T-121606.

Molecular-genetic analyses revealed candidate molecules from a series of ABC transporters and the DNA repair system for more detailed studies of their function in the development of multidrug resistance. *In vitro* and *in vivo* experiments showed the efficacy of new taxane derivatives in the model of paclitaxel resistant ovarian carcinoma compared to paclitaxel.

Key words: ovarian carcinoma, multidrug resistance, biomarker, therapy response, taxanes