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BRCA mutation and castration-resistant prostate cancer, association with the AKT/m-TOR signaling cascade

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Motivation and Aim: Mutations of BRCA genes are an independent poor prognostic factor in the development of prostate cancer [1]. It is believed that its effect on the prognosis is higher than the degree of differentiation, stage, level of the prostatic specific antigen. It is known that the mutations BRCA1/2 are most often associated with the AKT/m-TOR signaling cascade hyperactivation [2–4]. The purpose was to study the AKT/m-TOR pathway components in castration-resistant prostate cancer patient, depending on the presence of the BRCA mutations.
Methods and Algorithms: 40 patients with prostate cancer, 15 patients with castration-resistant prostate cancer and 20 patients with benign hyperplasia are enrolled in the investigation. The expression of AKT, c-Raf, GSK-3, PDK1, and m-TOR, 70-S64, E-BP1 was determined by real-time PCR. The BRCA 1/2 mutation was determined in allele-specific PCR in real time.
Results: Activation of the AKT/m-TOR signaling cascade was detected in prostate cancers. The high levels of AKT and m-TOR expression were revealed. The increase in the level of phosphatase PTEN was found in benign hyperplasia and cancer tissues [5]. The level of mRNA 4E-BP1 was decreased in castration-resistant prostate cancer patients. At the next stage of the study, the incidence of inherited BRCA 1/2 mutations were studied in patients with castration-resistant cancer. The *BRCA1-5382insC* mutation was detected in 3 patients (20 %), *BRCA1-4153delA* – in 5 patients (33 %), *BRCA1-185delAG* – in 2 patients (13 %), *BRCA1-T300G* – in 2 patients (13 %) and *BRCA2-6174del* – in 4 patients (27 %). BRCA1-deficiency activates the AKT oncogenic pathway, one of the most common alterations associated with human malignancy. Mutation of *BRCA1* gene increases the phosphorylation and the kinase activity of AKT. The decreased AKT expression in cancers was found in patients with *BRCA1-5382insC* mutation. Mutation of *BRCA1-4153delA* increased expression of 70S, m-TOR, in the presence of *BRCA1-T300G* – increased PTEN. The inherited *BRCA2-6174del* mutation was correlated with the increased expression of AKT.
Conclusion: Therefore, the development of PCa is accompanied by activation of this signaling cascade, even more pronounced in the presence of mutations *BRCA2-6174del*, *BRCA1-4153delA*, *BRCA1-T300G*. It should be noted that the frequency of occurrence of these mutations varies from 13 to 33 %.

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