STRESZCZENIE W JĘZYKU ANGIELSKIM

Papillary thyroid cancer (PTC) is the most common endocrine cancer. Incorrect activation of the mitogen- activated kinase pathway through various genetic events is the main oncogenic process. The effect of the *BRAF V600E* mutation on the adverse pathological and clinical features of PTC, such as advanced Tumor-Node-Metastasis stage, the presence of cervical lymph node metastases or extrathyroidal extension has been described. Since 2013, there have been reports of exacerbating effects of mutations in the telomerase reverse transcriptase promoter (*pTERT*) on aggressive PTC phenotypes. The relationship between two (C228T or C250T) hotspot mutations of the *pTERT* and inferior clinical and pathological features, such as tumor diameter, extrathyroidal invasion, vascular invasion, distant metastases, disease recurrence, and patient death rate, has been demonstrated. There are reports in the literature that the coexistence of the *pTERT* and *BRAF V600E* mutations has a synergistic effect in increasing the aggressiveness of PTC.

The aim of the dissertation was to assess the frequency of coexisting *pTERT* and *BRAF V600E* mutations and their relationships with the clinical course of disease. The differences between the presence of a single mutation and the coexistence of both mutations and their relationship with clinical and pathological features were analyzed.

The study group included 568 unselected PTC patients with known *BRAF* status diagnosed between 2000 and 2012 at the Endocrinology Clinic of Holycross Cancer Center in Kielce.

Medical documentation was a source of data on histopathological and clinical features. DNA obtained from postoperative paraffin blocks was biological material for genetic analysis for the presence of mutations.

Data on the initial stage of the disease, response to treatment and the course of the disease were obtained from medical records. Genetic analysis was preceded by DNA isolation from a paraffin block using The Maxwell® 16 FFPE Tissue LEV DNA Purification Kit (Promega). Genetic analysis of *pTERT* and *BRAF V600E* was based on Sanger sequencing and the quantitative polymerase chain reaction (qPCR) method, respectively.

Associations between *BRAF V600E* and *pTERT* mutations and clinicopathological features were analyzed. The chi-square test (χ^2), Fisher exact test and Mann-Whitney U were applied for statistical analysis.

Median follow-up was 10 years. The *pTERT* mutations were detected in 13.5% (77/568) of PTC cases. The C228T and C250T *TERT* hotspot mutations were found in 54 (9.5%) and 23 (4%) patients, respectively. Coexisting *BRAF V600E* and *TERT* hotspot promoter mutations were detected in 9.5% (54/568) of patients, and significantly associated with gross extrathyroidal extension ($p = 0.003$), tumor stage pT3–4 ($p = 0.005$), stage II–IV ($p = 0.019$), intermediate or high initial risk ($p = 0.003$), worse than excellent response to primary therapy ($p = 0.045$), recurrence ($p = 0.015$), and final outcome of no remission ($p = 0.014$). Study results indicate that the coexisting *BRAF V600E* and *pTERT* mutations in patients with PTC are associated with poor initial prognostic factors and clinical course, and may be useful for predicting worse response to therapy, recurrence, and poor outcome.