Complex molecular diagnostics of gastrointestinal stromal tumors

ABSTRACT

Most of gastrointestinal stromal tumors (GISTs) are characterized by activating mutations in the *KIT* and *PDGFRA* genes (80 – 85 %). Mutations in the *BRAF*, *KRAS*, defects in the SDH complex or *FGFR1::TACC1*, *ETV6::NTRK3* fusions were detected in the group of *KIT/PDGFRA* non-mutated GISTs (10 – 15 %). Targeted therapy with Imatinib mesylate (IM) marked a significant breakthrough in treating GISTs. A significant problem with targeted therapy is the formation of primary or secondary resistance. The biological behavior of the GIST is unpredictable. Determining the activity of selected markers for cell proliferation and senescence will enable the objectification risk of tumor behavior's aggressivness. The aim of the first part of our work was the mutational analysis of the *KIT* and *PDGFRA* genes and the detection of secondary mutations in patients with disease progression. We detected primary mutations in *KIT* and *PDGFRA* genes in 83.5 % of samples. We also demonstrated the presence of secondary mutations in 16 patients with progression of disease (in 29 progressive lesions – 69 %). We confirmed significant intratumor and also intertumor heterogeneity of secondary mutations. The aim of the second part of the thesis was the analysis of alterations in the *KIT/PDGFRA* non-mutated GISTs. In this group of GISTs we demonstrated defects in the SDH complex subunits, mutations in the *BRAF* and *NF1* genes and alterations in the *AKT1* and *ATR* genes. The purpose of the last part of this work was the determination of mRNA expression levels of selected markers of proliferation and senescence. We found that expression levels of selected markers (Ki-67, TPX2, TOP2A and hTERT) are suitable markers for determining tumor proliferation and malignant potential of GIST. Additionally, we found a correlation between higher mRNA levels of proliferation markers Ki-67, TPX2 and hTERT and shorter survival in GIST patients (EFS and OS).

KEYWORDS

GIST, genes mutations, therapy resistance, tumor heterogeneity, proliferation markers