ABSTRACT

Neuroblastoma (NB) is a malignant embryonal tumor of the peripheral sympathetic nervous system derived from neural crest and is the most common tumor in infants. If the protooncogen *MYCN* is amplified in the case of high risk neuroblastoma, the current therapy fails. The biggest issue is the development of resistance. Ellipticine (ELLI) is a potential antineoplastic drug, whose cytotoxic effect is mainly based on the inhibition of topoisomerase II, its intercalation into the double helix structure of DNA and formation of adducts with DNA after enzymatic activation by cytochromes P450, peroxidases, sulfotransferases and N,O-acetyltransferases.

Long-term cultivation of NB cell line UKF-NB-4 with ELLI leads to resistance, which is multifactorial. (i) It appears that ELLI is not effluxed from cells of the line UKF-NB-4^{ELLI} as in the case of doxorubicin resistance in UKF-NB-4, but is transported from the nucleus and sequestrated in intracellular compartments. Cytotoxicity of ELLI is reduced also by (ii) low intracellular pH and (iii) decreased expression of topoisomerase II. (iv) Expression of enzymes activating ELLI is unchanged on the mRNA level detected by DNA microarray. However, enhanced expression of enzymes activating ELLI (cytochrome P450 3A4 and cyclooxygenase-1) is detected by qRT-PCR. Moreover expression of cytochrome b_5, which enhances the efficiency of activation of ELLI with cytochromes P450 1A1/2 and 3A4, is increased. (v) Expression of *MYCN* is reduced. However, in the second stage of cultivation UKF-NB-4 cells with ELLI there is a disruption of self-expression feedback of *MYCN* and the translocation of MYCN protein back into the nucleus is induced. (vi) There is reduced apoptosis induced by ELLI and reduced proliferation. At the same time the cells partially differentiate. (vii) UKF-NB-4^{ELLI} cells resistant to ELLI induce angiogenesis and have higher metastatic potential than the parental line UKF-NB-4.

Using gene expression profiling of the cells UKF-NB-4^{ELLI} (in comparison to parental line) may therefore determine that access to the targets of cytotoxic action of ELLI is limited and the malignant phenotype of UKF-NB-4^{ELLI} is supported. Suprisingly, expression of enzymes activating ELLI has not decreased, and some even increased. *(In Czech)*

Keywords: neuroblastoma, ellipticine, mechanism of resistance, expression profiling, anticancer drug