Summary

This thesis focuses on drug-resistance in childhood cancer and detection of cytogenetic changes related to it. High-risk forms of childhood cancer often require the use of high doses of chemotherapy, which can lead to drug-resistance. Detection of chromosomal aberrations of drug-resistant tumors may contribute to the prognosis and prediction of treatment.

Most of the results came from studying neuroblastoma (NBL). Other results represent genetic changes in Ewing's sarcoma and pediatric pheochromocytomas. For the study of chromosomal aberrations we used comparative genomic hybridization (CGH) and array CGH examination supplemented using multicolor or interphase fluorescence *in situ* hybridization. Changes in mRNA expression were investigated using expression array analysis complemented by quantitative polymerase chain reactions, changes in protein expression were examined using western blotting or flow cytometry.

This thesis is an annotated collection of six articles. The study of chromosomal aberrations in Ewing sarcomas represents a literature review, together with our results. The study on pheochromocytoma represents one of the largest sets of chromosomal aberrations in pediatric pheochromocytomas. The most extensive part of the thesis is based on monitoring cytogenetic changes in NBL. Long-term cultivation with ellipticine has produced a resistant cell line that we compared with parental one. We detected cytogenetic changes, as well as changes in mRNA expression and that of selected proteins. We found that ABC transporters did not contribute to ellipticine-resistance, whereas up-regulation of topoisomerases played a significant role as did up-regulation of Bcl-2. The last part focuses on the *MYCN* oncogene amplification - the most important prognostic factor relative to NBL. We demonstrated that cytostatics induced expulsion of amplified *MYCN* copies from the chromosomal homogeneously staining regions. Additionally, we found that long-term cultivation with cytostatic agents increased the expression of MYCN, which can be considered to be characteristic of drug-resistant NBL cells. These results could be clinically significant because the *MYCN* is being considered as a target for NBL therapy.

The results presented in this thesis extend the knowledge regarding genetic changes and mechanisms of drug-resistance in pediatric cancers. The work confirms that drug-resistance of tumor cells is associated with complex mechanisms that complement each other. Therefore overcoming this problem will involve a comprehensive and multifaceted approach.