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The effect of tyrosine kinase inhibitors in high-grade glioma patient-derived cells

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Background: High-grade gliomas are the most frequently diagnosed malignant brain tumors in adults, with a very unfavorable prognosis. Although various strategies have been applied in the clinical setting, no significant progress has been made in the treatment of high-grade glioma. Clinical trials continue to expand into new approaches such as targeted agents and immunotherapy. Here, we performed pharmacological screening of tyrosine kinase inhibitors (TKIs) on patient-derived glioma cells *ex vivo* and assessed the expression of multidrug resistance (MDR) marker in glioma and stromal (non-glioma) cells. The effects of TKIs have been compared with chemotherapeutic agents approved for the treatment of high-grade glioma. **Material and Methods:** Primary patient-derived cell cultures were established from resections of high-grade gliomas. After short-term culturing (2-3 weeks), a mixed population of glioma and non-glioma cells was treated with 4 TKIs (alectinib, dabrafenib, trametinib, and nintedanib), as well as temozolomide (TMZ) and carmustine (BCNU). The maximum achieved concentration in human plasma during therapy (Cmax) was set as the upper limit and 4 lower concentrations were also used during the study. An immunofluorescence assay allowing discrimination of glial fibrillary acidic protein antibody-positive glioma cells versus negative non-glioma cells was performed using an ImageXpress Pico high-content imager (Molecular Devices) with CellReporterXpress 2.9 software. The MDR marker (ABCB1) was analyzed with the corresponding antibody in the same immunoassay. **Results:** Among the compounds tested, alectinib and TMZ did not affect cell growth and did not change the number of ABCB1-positive cells. Other compounds significantly inhibited the growth of glioma cells. However, they were not selective towards glioma cells, on the contrary, they showed greater cytotoxicity in non-glioma cells. The number of glioma cells positive for the ABCB1 marker increased significantly after treatment with dabrafenib, nintedanib, and BCNU, while trametinib and did not change ABCB1 expression in glioma cells. Stromal (non-glioma) cells generally followed the pattern of ABCB1 observed in glioma cells. **Conclusions:** Novel functional immunoassay may provide valuable information on the sensitivity of high-grade gliomas to different TKIs and possible treatment outcomes based on the expression of MDR marker.
Keywords: ABCB1, high-grade glioma, immunoassay, patient-derived cell culture, tyrosine kinase inhibitors

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The significance of interleukin-8 in hormonally dependent early breast cancer – association with the established parameters ER/PR and HER2

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Background: Interleukin-8 (IL-8) is a multifunctional cytokine linked to cancer progression. Studies have confirmed high IL-8 levels in HER2-enriched and basal-like (ER–) primary breast tumors. The aim of this study was to evaluate the relationship between intratumoral IL-8 protein levels and clinical outcome in hormone dependent (ER+) primary breast cancer patients. **Patients and methods:** The study included 65 early-stage breast cancer patients with detectable levels of hormone receptors (ER>0, PR>0), all of whom had not received any prior hormonal or chemotherapeutic systemic therapy. The median follow-up was 144 months. Steroid hormone receptor status was determined by ligand-binding assay. HER2 status (absence or presence of gene amplification) was determined by chromogenic in situ hybridization (CISH). IL-8 protein levels were determined in cytosol tumor extracts by quantitative ELISA. ER level of 10 fmol/mg, PR level of 20 fmol/mg and the median IL-8 concentration level of 88.8 pg/mg, were used as cut-off values. **Results:** There was a significant difference in relapse free survival (RFS) between IL8low and IL8high subgroups of patients (Log rank test, p=0.002). Considering subgroups of patients stratified in different phenotypes according to receptor status and the median IL-8 value, if IL-8 is highly expressed, the influence of ER is weaker and there was no significant difference in RFS between subgroups with ERlowIL8high and ERhighIL8high phenotypes. The same is true for PR and HER2 and there was no significant difference in RFS between subgroups with PRlowIL8high and PRhighIL8high phenotypes, neither between subgroups with HER2−IL8high and HER2+IL8high phenotypes. On the other hand, subgroup with ERhighIL8low