Tobias W. Herion
Dr. med.

Investigations on the Combined Effects of TGF Beta Receptor Kinase Inhibition, Temozolomide and Radiation Therapy in the Treatment of Glioblastoma Multiforme in Vitro and in Vivo.

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Herr Prof. Dr. med. Dr. rer. nat. Peter Huber

This work investigated the effects of the novel dual transforming growth factor-β receptor I/II (TGF-βRI/RII) kinase inhibitor LY2109761 on glioblastoma multiforme when combined with the present clinical non-surgical standard combination regimen of radiotherapy plus temozolomide. Human glioblastoma U87MG (methylated MGMT promoter), T98 (unmethylated MGMT promoter) and endothelial cells (HUVECs) were treated with combinations of LY2109761 ± temozolomide ± radiation. We found that LY2109761 reduced clonogenic survival of U87MG and T98 cells and further enhanced the radiation-induced anticlonogenicity. In addition, LY2109761 had antimigratory and antiangiogenic effects in Matrigel migration and tube formation assays. In vivo, in human U87MG xenograft tumors growing subcutaneously on BALB/c nu/nu mice, LY2109761 delayed tumor growth alone and most of all in combination with fractionated radiation and temozolomide. Interestingly, as expected, the methylated U87MG model was more sensitive to temozolomide than the unmethylated T98 model in all experiments, whereas the opposite was found for LY2109761. Moreover, with respect to tumor angiogenesis, while LY2109761 decreased the glioblastoma proliferation index (Ki-67) and the microvessel density (CD31 count), the relative pericyte coverage (α-SMA/CD31 ratio) increased in particular after triple therapy, suggesting a vascular normalization effect induced by LY2109761. This normalization could be attributed in part to a decrease in the Ang-2/Ang-1 messenger RNA ratio. LY2109761 also reduced tumor blood perfusion as quantified by noninvasive dynamic contrast-enhanced magnetic resonance imaging. Together, the data indicates that the addition of a TGF-βRI/RII kinase inhibitor to the present clinical non-surgical standard (radiotherapy plus temozolomide) has the potential to improve clinical outcome in human glioblastoma. It provides a rationale to evaluate this or similar strategies in clinical trials.