Half-time review – Abstract

Title. Improved treatment for brain tumor patients – intratumoral cytostatic drugs and immunotherapy.

Background. Advances in surgery, chemo- and radiotherapy have only modestly improved survival rates in brain tumor patients during the last decades. Emerging evidence suggests that an effective treatment of brain tumors will likely require treatment of multiple aspects of tumor pathobiology in order to overcome tumor heterogeneity and tumor immunosuppression. We propose that intratumoral delivery of cytostatic drugs and immunotherapy, could represent a new tool to treat brain tumors. Systemically delivered chemotherapeutic drugs come with severe side effects, high levels of toxicity and have to overcome the blood-brain barrier to reach the tumor. Intratumoral administration of cytostatic drugs, also referred to as convection-enhanced delivery (CED) is a technique to increase the drug distribution within the tumor and can circumvent these problems.

Methods. Plasma samples from pediatric brain tumor patients where immune-profiled using cytokine multiplex assays, in order to identify inflammatory mediators which could serve as potential peripheral biomarkers before and during immunotherapy. In rodent models of malignant brain tumors chemotherapeutic drugs were delivered intratumorally with mini-osmotic pumps and an autologous whole cell vaccine were used to generate a specific cytotoxic CD8 effector cell immunity. Treatment efficacy of clinically relevant cytostatic drugs and immune-related mechanisms in immunocompetent and immunocompromised mice carrying brain tumors (GL261, KR158) was investigated.

Preliminary results. We identified patient groups with distinct preoperative inflammatory cytokines profiles that could be used as biomarkers to help design, predict or follow immunotherapy in children with brain tumors. In mouse glioma models intratumoral cytostatic drugs and CED of temozolomide and cisplatin were tolerated and could achieve prolonged survival and cure. CED of temozolomide cured GL261-bearing mice and acted synergistically with wildtype immunization. CED of temozolomide had no effect in the more aggressive KR158 model, although wildtype immunization alone slightly prolonged survival. Both locally delivered cisplatin and temozolomide depend on an intact immune function to exert its effect but the former had no additive effect with either GL261 wild-type- or GL-GM-based immunotherapy.

Significance. Our results have important implications for the future development and implementation of locally administered cytostatic drugs and immunotherapy against malignant brain tumors.