in combination with cytotoxic agents. Unfortunately, in the clinic, anti-angiogenic therapy has not yet met initial expectations despite high radiological response rates. The direct anti-tumour effect of anti-angiogenic drugs is not clear and eventually all GBMs recur, indicating that the tumours develop escape mechanisms towards treatment.
In a series of preclinical studies using intracranial patient-derived xenografts, we have shown that such escape mechanisms are associated with a metabolic switch in the tumours towards glycolysis, as indicated by an up-regulation of the transcription factor HIF-1 (hypoxia inducible factor-1) and several metabolites associated with the glycolytic pathway (e.g. lactate). In conclusion, we have identified in a robust preclinical model system, specific biological escape mechanisms towards anti-angiogenic therapy, and based on this information novel therapeutic principles will be discussed.

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Targeting Angiogenesis in Glioma − Challenges and Pitfalls

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Malignant gliomas, notably glioblastoma are among the most vascularized and angiogenic cancers, and microvascular proliferation is one of the hallmarks for the diagnosis of glioblastoma. Angiogenesis is regulated by a balance of pro- and antiangiogenic signals; overexpression of VEGF and activation of its receptors, most notable VEGFR-2 and -3, results in endothelial cell proliferation and leaky vasculature. Heterogeneous perfusion and oxygenation, peritumoral edema and increased interstitial pressure are the consequence. Both endothelial and tumour cells are strongly dependent on integrin-mediated adhesion for cell proliferation, survival, migration and invasion.
Strategies aiming at inhibition of cell signaling and angiogenesis, including integrin inhibitors, have been clinically investigated in gliomas over the last 5 years. Radiological responses, a decreased requirement of corticosteroids and temporary improvement in performance status have repeatedly been observed. Toxicity was mild-moderate and manageable, notably there was no evidence for a substantially increased incidence of intracranial bleeding. However definitive comparative (randomized !) investigation has failed to demonstrate improved outcome with single agent inhibition of EGFR, or PDGFR or VEGF/VEGFRs pathways in recurrent glioblastoma. Definitive phase III trials combining the anti-VEGF monoclonal antibody bevacizumab, or cilengitide, a peptidic integrin-inhibitor, together with temozolomide and radiotherapy are ongoing (accrual completed).
The integration of anti-angiogenic strategies in the management of malignant glioma also poses entirely new challenges in patient management: 1) Many agents are known for increasing the risk of thrombosis, embolism and intracranial bleeding. 2) Evaluation of treatment efficacy is difficult and new biomarkers of activity, including functional, metabolic or molecular imaging techniques are urgently needed. Normalization of vasculature leads to decrease in contrast enhancement without necessarily reflecting tumour shrinkage. Tumour heterogeneity, putative prognostic or predictive factors require early controlled trials, novel trial designs and endpoints. 3) Activation of alternate pathways and tumour escape mechanisms may require combination of multiple agents, which is often not feasible due to regulatory restrictions and potential complex toxicities. Emerging clinical and experimental evidence suggests that anti-angiogenic drugs might need to be combined with drugs targeting tumour adaptive mechanisms in addition to cytotoxic chemotherapy and irradiation for a maximal antitumour effect.

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Clinical

Abstract not received

Scientific Symposium (Mon, 26 Sep, 09:00−11:00) **The Role of IGFs/IGF-1R Pathway in Paediatric Malignancies**

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Biology of IGF/IGFR Pathway in Sarcomas

Abstract not received

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IGF1R Inhibitors in the Treatment of Ewing Sarcomas

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IGF signaling has been shown to play a role in a variety of pediatric sarcomas, including Ewing's sarcomas. While no genetic alterations in IGFIR have been identified, epigenetic changes in the form of loss of imprinting of the ligand, IGF-2, have been found in Ewing's sarcomas. These findings led to clinical studies testing a variety of IGFIR humanized antibodies in patients with recurrent Ewing's sarcomas. The Sarcoma Alliance for Research through Collaboration (SARC) initiated an international study utilizing the fully human IGFIR antibody R1507, in collaboration with Roche. We entered 132 unselected patients with recurrent Ewing's sarcoma from December 18, 2007 through April 4, 2010, and 115 patients were eligible for evaluation. Most patients were treated at a dose of 9 mg/kg as a weekly IV infusion, and five patients were treated with a dose of 27 mg/kg given every three weeks as an IV infusion when an amendment was included to test this dose at the end of the study. Overall, objective responses were seen in 19 patients for a RR of 16.5% including two CRs. Eight of the 19 responses lasted greater than 18 weeks, and 11 responses lasted less than 18 weeks. Most responses developed rapidly after initiating therapy, although there was at least one patient who developed a PR after more than 20 weeks of treatment. Patients tolerated therapy extremely well. The common Grade 3/4 toxicities observed included thrombocytopenia 7%, anemia 7% and hyperglycemia of 3%. We have created models to study the effects of IGFIR antibody treatment in mice and have identified factors that likely influence response. First, IGFIR density is quite variable in the surface of tumours, and tumours with very low density IGFIR do not respond to IGFIR Ab treatment. Second, similar to patients treated on this study, responding tumours eventually re-grow and this tumour re-growth corresponds with re-activation of pAKT, in the setting of continued IGFIR suppression. Thus we hypothesize that activation of "by pass" pathways leads to recurrence in responding patients. We still need to identify positive predictors of response and are engaged in analyzing patient samples treated on this study do so. Finally, we are using our preclinical models to identify combination therapy that might mitigate activation of "by pass pathways and these will be discussed.

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IGF1R Targeting in Non-sarcoma Pediatric Malignancies

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Insulin-like growth factors and their receptor insulin-like growth factor type 1 receptor (IGF-1R) are implicated in tumour growth, metastatic dissemination and drug resistance, and thus represent a promising therapeutic target in cancer. Physiological cell growth is widely regulated by growth factors such as IGF1 and IGF2, and normally down-regulated after growth. In multiple cancer cells, particularly pediatric cancers, this growth factor pathway is activated. Whereas *IGF-1R* gene mutations or gene amplification appear rarely, loss of imprinting of IGF2 (11p15) have been reported occurring in rhabdomyosarcoma, neuroblastoma, hepatoblastoma, nephroblastoma; elevated IGFBP-3 levels are found associated with EWS-FLI transfusion products in Ewing sarcoma. *MYCN* overexpression modulates IGF action through increased IGF-1R expression and decreased IGF-BP3 expression, resulting in increased tumorigenicity in neuroblastoma. In Wilms' tumours, mutations/deletions in WT1 result in overexpression of IGF-1R and IGF-II; the prior was found associated with relapsed disease. IGF-1R targeting using IGF1R antisense, different monoclonal antibodies or small molecule tyrosine kinase inhibitors has been explored preclinically in osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and neuroblastoma mostly showing anti-proliferative effects *in vitro* and growth inhibition in xenografts *in vivo*, Enhanced effects were observed when IGF1R targeting was combined with classical anticancer agents or other growth factor receptor or downstream pathway inhibitors such as PI3K, AKT or mTOR. The clinical evaluation