

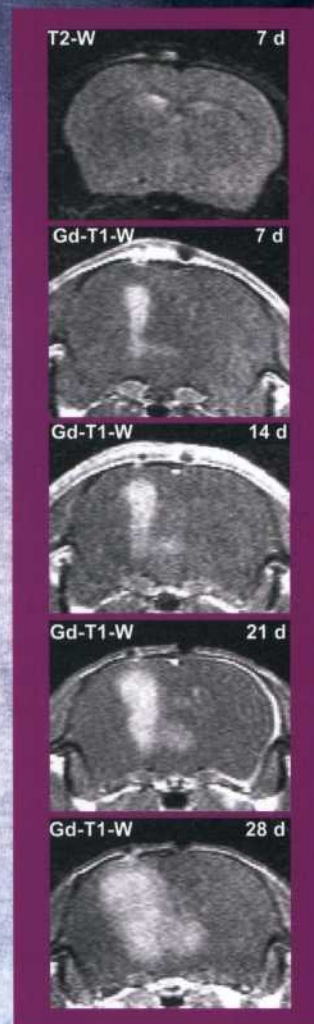
Neuro-Oncology

**Basic and Translational
Investigations**

Clinical Investigations

Review

Abstracts from the World
Federation of Neuro-Oncology
Second Quadrennial Meeting
and the Sixth Meeting of
the European Association for
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tumor and the pia, had the fibrous morphology of reactive astrocytes, and some of these cells were also GFAP-ir. The presence of proliferating cells was probed using antibody to PCNA (Chemicon MAB424). In addition to the tumor cells, PCNA-ir was observed in subpopulations of nestin-ir presumptive NPCs and in nestin-ir presumptive reactive astrocytes, as well as in unidentified non-nestin-ir cells dispersed lateral to the ventricle, in the corpus callosum, in the fimbria, and in the dentate gyrus. Our results suggest that the experimental glioma induced appearance of proliferating nestin-ir NPCs, nestin-ir reactive astrocytes, and other cells whose identity has not yet been determined. The position of the reactive astrocytes suggests that mechanical deformation may play an inductive role. NPCs near the ventricle and medial to the tumor mass may be responding to presently unidentified factors emerging from the tumor and/or from adjacent host cells. In neither case did it appear that the tumor environment was highly mitogenic for host cells, which suggests that host cells were not major contributors to the tumor burden.

70. TARGETED THERAPY WITH ANP IN CHILDREN LESS THAN 4 YEARS OLD WITH INOPERABLE BRAIN STEM GLIOMAS

S.R. Burzynski, R.A. Weaver, T.J. Janicki, B. Burzynski, and G. Jurida; Burzynski Clinic, Houston, Texas, USA

The purpose of the study is to evaluate the outcome of patients less than 4 years old with intrinsic diffuse brain stem gliomas (BSG) treated with ANP (antineoplastons A10 and AS2-1) in two FDA and Institutional Review Board monitored phase 2 trials. A total of 10 assessable patients who were less than 4 years old were among 65 participants of phase 2 trials (study and special exception patients): 2 with anaplastic astrocytomas, 1 with pilocytic astrocytoma, and 7 who had no biopsy because of a dangerous tumor location. Age ranged from 3 months to 3 years. Three patients failed prior radiation and chemotherapy, 1 had stable disease after radiation, 2 had tumor resection, and 4 were not treated prior to ANP. ANP was given intravenously daily through a subclavian venous catheter and a double channel infusion pump. The median duration of ANP administration was 9½ months, and the average dosage of A10 was 12.16 g/kg/day and of AS2-1 was 0.41 g/kg/day. Responses were assessed by gadolinium-enhanced MRIs and confirmed by PET scans in some cases. The overall survival at 2 years was 50% and at 5 years 20%, and the maximum survival is 6+ years. Median progression-free survival was 2 years and 2 months. Complete response was achieved in 30%, stable disease in 40%, and progressive disease in 30%. Serious toxicities included reversible anemia and hypokalemia. There were no chronic toxicities. ANP targets the *AKT2*, *RAS*, *p53*, and *p21* pathways, and its administration results in substantial survival and response rates in a small group of young children who do not have a favorable prognosis for standard therapy.

71. INHIBITION OF INSULIN-LIKE GROWTH FACTOR I RECEPTOR SIGNALING INCREASES CHEMOSENSITIVITY OF PEDIATRIC CNS ATYPICAL TERATOID/RHABDOID TUMOR CELLS

T. Shalaby, J. D'cunia, and M. Grotzer; University Children's Hospital, Oncology, Zurich, Switzerland

Central nervous system (CNS) atypical teratoid/rhabdoid tumors (ATT/RhT) are among the pediatric malignant tumors with the worst prognosis and fatal outcome. To date there are no explanations for their remarkable resistance to cytostatic drugs and radiotherapy. Insulin-like growth factor I receptor (IGF-IR) protects cancer cells from apoptosis induced by a variety of anticancer drugs and radiation, but when impaired by inhibitors, tumor cells undergo massive apoptosis, resulting in an inhibition of tumorigenesis and metastases in experimental animal models. IGF-IR was found to be clearly overexpressed in ATT/RhT compared to near normal brain samples and to other pediatric CNS neoplasms as confirmed by Western blotting and immunohistochemistry. Moreover, we found IGF-I and IGF-II mRNA in an ATT/RhT cell line indicating the presence of an autocrine/paracrine IGF-I/II/IGF-IR loop in ATT/RhT. Human BT-12 and BT-16 ATT/RhT cells were treated with IGF-IR antisense or scrambled control oligonucleotides for different time periods. Antisense treatment of ATT/RhT cells for 48 h resulted in significant downregulation of IGF-IR mRNA and IGF-IR protein expression, both in BT-12 and in BT-16 cells. IGF-IR antisense treatment resulted in inhibition of cellular proliferation and induction of apoptosis. Moreover, chemosensitivity of ATT/RhT cells to doxorubicin and cisplatin was found to be significantly increased upon treatment with IGF-IR antisense oligonucleotides. This suggests the presence of an autocrine/paracrine IGF-I/II/IGF-IR loop in ATT/RhT that may be responsible for the low susceptibility of ATT/RhT cells to undergo apoptosis. Inhibition of IGF-IR represents a novel therapeutic strategy in childhood CNS ATT/RhT that warrants further investigation.

72. HYPOXIA SENSITIZES HUMAN MALIGNANT GLIOMA CELLS TOWARD CD95L-INDUCED CELL DEATH

J. Steinbach,¹ H. Wolburg,² A. Klumpp,¹ and M. Weller;¹ Abt. Allgemeine Neurologie and ²Institute of Pathology, University of Tübingen, Tübingen, Germany

Death ligands such as CD95 ligand (CD95L) have limited activity against glioma cells under normoxic conditions (Weller et al., J. Clin. Invest. 94, 954, 1994). However, many glioma cell lines can be sensitized toward death ligand-induced apoptosis by inhibition of epidermal growth factor receptor (EGFR) (Steinbach et al., Brain Pathol. 12, 12, 2002). Hypoxia is a critical aspect of the microenvironment of gliomas. We have established a paradigm for the investigation of hypoxia-induced cell death in glioma cells in vitro, which faithfully reproduces many aspects of human glioma pathology (Steinbach et al., Cell Death Differ. 10, 823, 2003). Here, we investigated the effect of co-exposure to acute hypoxia and CD95L in three human malignant glioma cell lines with different susceptibility to CD95L under normoxic conditions. Hypoxia sensitized all three cell lines toward CD95L-induced cell death. Co-exposure resulted in apoptotic changes in the early phase, with gradual conversion to secondary necrosis with increasing length of hypoxia. The mitochondrial injury induced by hypoxia was enhanced by co-treatment, and caspase cleavage became prominent. Inhibition of the EGFR, while sensitizing glioma cells to CD95L under normoxia, protects glioma cells from hypoxia by reducing energy consumption (Steinbach et al., Cancer Res. 64, 1575, 2004). However, the opposing effects of EGFR signaling on death induced by CD95L or hypoxia were neutralized by co-exposure to hypoxia and CD95L. Further, inhibition of protein synthesis by cycloheximide also reduced glucose consumption and conferred protection from hypoxia, but did not modulate CD95L-induced cell death under hypoxic conditions. These results suggest that death ligands may be useful to target hypoxic tumor cells resistant to conventional therapies or to complement strategies aiming at the induction of tumor hypoxia.

73. CONSTITUTIVE INTEGRIN ACTIVATION BY RAP-GTPASE ON LEUKEMIC CELLS PROMOTES PROGRESSION OF LEPTOMENINGEAL LEUKEMIA

D. Brandsma,^{1,2} L. Ulfman,³ J. Reijneveld,¹ M. Bracke,⁴ M. Taphoorn,¹ J. Zwaginga,^{6,7} M. Gebbink,⁵ H. de Boer,⁸ and E. Voest;² Departments of ¹Neurology, ²Medical Oncology, ³Pulmonary Diseases, ⁴Pharmaco-epidemiology and Pharmacotherapy, and ⁵Haematology, University Medical Center Utrecht, Utrecht; ⁶Department of Haematology, Academic Center Amsterdam, Utrecht; ⁷Sanquin Research, Amsterdam; ⁸Department of Nephrology, Leiden University Medical Center, Leiden; The Netherlands

Leptomeningeal metastases are a serious neurological complication in cancer patients and are associated with a dismal prognosis. Tumor cells that enter the subarachnoid space adhere to the leptomeninges and form tumor deposits. The role of integrins in tumor cell adhesion to leptomeninges is largely unknown. We studied the role of integrin expression and activation in the progression of leptomeningeal metastases. Therefore, we used a suspension (L1210-S) and an adherent (L1210-A) variant of a mouse acute lymphocytic leukemic cell line. Static adhesion levels of L1210-A cells on a leptomeningeal cell layer were significantly higher than for L1210-S cells. All mice that were intrathecally injected with L1210-A cells died rapidly because of leptomeningeal leukemia. In contrast, 45% of long-term survivors were seen after intrathecal injection with L1210-S cells. β_1 -, β_2 - and β_3 -integrins were in a constitutive active state on L1210-A cells and in a low but inducible state on L1210-S cells, as determined by adhesion assays on surfaces coated with β_1 integrin ligand (collagen), β_2 integrin ligand (ICAM-1), and β_3 integrin ligand (vitronectin). Expression levels of these integrins were comparable in the two cell lines. The discrepancy in integrin activation state on the two cell lines is due to a difference in the activation of the small GTPase Rap, which is involved in integrin inside-out signaling. Rap in L1210-A cells is in a constitutive active state, whereas in the L1210-S cells Rap is off, but inducible. Our data indicate that constitutive integrin activation on leukemic cells promotes leptomeningeal leukemia progression by increased adhesion to the leptomeninges via an aberrantly regulated Rap GTPase signaling pathway.