TARGETED DOWNREGULATION OF TGF-BETA2 AS IMMUNOTHERAPY FOR MALIGNANT GLIOMA: A PHASE IIb STUDY

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High-grade (malignant) glioma are highly aggressive tumors showing marked overexpression of transforming growth factor-beta2 (TGF-beta2). TGF-beta plays a key role in malignant progression by inducing proliferation, invasion and metastasis, angiogenesis and immunosuppression and is responsible for the immunodeficient state of malignant glioma patients. AP 12009, a phosphorothioate antisense oligodeoxynucleotide specific for the human TGF-beta2 mRNA, has been developed as a targeted anti-tumor therapy. AP 12009 has already proven safety and shown anti-tumor activity in phase I/II clinical studies as therapy for recurrent high-grade glioma after intratumoral infusion. Based on the successful phase I/II studies with AP 12009 a phase IIb multinational study in adult patients with recurrent high-grade glioma, i.e. Anaplastic Astrocytoma (AA), WHO grade III, and Glioblastoma Multiforme (GBM), WHO grade IV, is currently ongoing. Patients are randomized into 3 treatment groups to receive either one of two doses of AP 12009 or standard chemotherapy, i.e. temozolomide, or the combination Procarbazine/CCNU/Vincristine (PCV). The primary objectives of this open label, phase IIb study are response rate (RR), progression free survival (PFS) and overall survival at different time points. AP 12009 is administered intratumorally as continuous high-flow microperfusion for 7 days every other week for up to 11 cycles. Both, efficacy and safety will be used as criteria for evaluation. In the previous phase I/II studies the median overall survival time was longer than the one reported in the recent literature (Yung et al., 2000, Theodosopoulus et al., 2001, Chang et al., 2004) on standard chemotherapy. Data on anti-tumor activity in phase I/II studies with 24 patients included several patients with stabilizations and two patients with complete tumor remissions, both of them long-lasting without recurrence. In the current phase IIb-study more than 120 patients have been enrolled. Based on the clinical data in malignant glioma and very encouraging preclinical results in pancreatic carcinoma AP 12009 is now in phase IIb studies in pancreatic carcinoma as its second tumor indication.

INCREASED ANTITUMOR EFFECTS OF INTRACAROTID CHEMOTHERAPY WITH PLATINUM DERIVATIVES IN EXPERIMENTAL C6 AND RG2 GLIOMAS AFTER BBB OPENING WITH 1-O-PENTYLGLYCEROL AND 2-O-HEXYLDIGLYCEROL

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Chemotherapy of malignant brain tumors is characterized by low cure rates resulting from ineffective concentrations of anticancer agents within the lesion and surrounding brain. Intracarotid alkylglycerols have been shown to increase the delivery of various cytotoxic drugs to brain tumors and to the normal brain adjacent to tumor. We have investigated the antitumor effects of a single intracarotid chemotherapy with cisplatin (2 to 4 mg/kg) or carboplatin (20 mg/kg) in C6 or RG2 glioma bearing rats. After stereotactic tumor implantation, platinum derivatives were given 5 (RG2) or 6 days (C6) later either in the absence or in the presence of 1-O-pentylglycerol (PG) or 2-O-hexyldiglycerol (HG). Intracarotid chemotherapy with cisplatin and carboplatin resulted in at least partial tumor regression in both glioma models. After chemotherapy in conjunction with blood-brain barrier (BBB) opening with PG and HG, the tumor response was stronger than after i.a. chemotherapy without alkylglycerols. In C6 glioma bearing rats treated with cisplatin (4 mg/kg) and 120 mM PG, long-term survival was observed (42 % (5 of 12 rats), p<0.05, logrank test), whereas all animals treated with cisplatin alone or controls without chemotherapy died. Intracarotid carboplatin in the presence of HG resulted in a significant increase in survival of Fischer rats with RG2 gliomas as compared to carboplatin without HG (p<0.05, logrank test). The treatment effects were also assessed by imaging with MRI and volume CT at day 13 after implantation of RG2 gliomas. Cisplatin seemed to be more effective than carboplatin in our system, however, it was associated with considerable nephrotoxicity. Taken together, BBB opening with PG and HG increased the antitumor effects of intracarotid platinum derivatives. Thus, i.a. chemotherapy in conjunction with short chain alkylglycerols represents a promising new strategy in the treatment of brain tumors.

Supported by Deutsche Krebshilfe (10-1995-Er 3).
PHASE II STUDY OF H-R3 MONOCLONAL ANTIBODY (NIMOTUZUMAB) AGAINST THE EGF RECEPTOR IN THE TREATMENT OF RESISTANT OR RELAPSED HIGH-GRADE GLIOMAS IN CHILDREN AND ADOLESCENTS

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Background. Despite aggressive treatment with multimodal therapy most children with high grade gliomas (HGG), including glioblastoma multiform (GM), anaplastic astrocytoma (AA) and intrinsic pontine glioma (PG) have a poor prognosis. Therefore, novel therapeutic approaches like the treatment with inhibitors of the EGFR tyrosine kinase have to be evaluated. The epidermal growth factor receptor (EGFR or ERBB1) believed to play a major role in the pathogenesis of gliomas is overexpressed in up to one-half of adults HGG and in about 30% of pediatric HGG (1). Nimotuzumab is a humanized monoclonal antibody that binds to EGFR and inhibits signal transduction. In preclinical experiments, Nimotuzumab demonstrates remarkable anti-proliferative, pro-apoptotic and anti-angiogenic effects on EGFR expressing tumors.

Purpose. This multicentre phase II trial was designed to explore the feasibility and efficacy of this H-R3 monoclonal antibody in the treatment of resistant and relapsed HGG in children and adolescents.

Patients and Methods. Pediatric patients with GM or AA confirmed by reference histopathology (except of PG without initially biopsy), with radiologically proven progressive disease following primary or relapse treatment and an expected lifespan of at least four weeks were eligible to the study. The treatment consisted of an induction therapy including a weekly short infusion (30 min) of 150 mg/m² Nimotuzumab for six weeks, and in case of non-PD a consolidation therapy of four infusions of the same dose in a three week interval. The response was documented by MRI in week 8 and 21 after start of therapy and evaluated using the RECIST-criteria (2) or only clinically in rapidly progressive disease.

Results. Between June and December 2004 18 patients aged 5.1 to 17.3 years (median 11.4 years) were enrolled in this study. So far 13 out of 18 patients are evaluable for response after the induction therapy. According to the RECIST criteria 5 out of these 13 patients showed SD in the MRI of week 8 with changes in the largest diameter of the index lesion by +16%, 0%, -10%, -12%, -25% accompanied by clinical deterioration in one patient and markedly clinical improvement in two patients. Surprisingly three of these 5 SD were seen in patients with PG. Four patients have already continued with the consolidation therapy. Two of them are evaluable for response in week 21 with one PR and one PD. Three of the 13 patients being evaluable for response after induction therapy are free of progression for 2.5, 3 and 7 months. The therapy with h-R3 monoclonal antibody was very well tolerated by all patients. No severe side effects related to the study medication were seen. All clinical deteriorations were associated with tumor progression or other concomitant diseases (one bacterial and one viral infection).

Conclusions. These data suggest that the repeated application of Nimotuzumab is well tolerated and safe. It has cytotoxic efficacy in heavily pretreated relapsed HGG, especially in intrinsic pontine glioma. A further trial using the Nimotuzumab in combination with radiotherapy in pediatric HGG should be warranted.

THE P-GP MODULATORS ELACRIDAR AND TARIQUIDAR ENHANCE THE PACLITAXEL CONCENTRATION IN THE BRAIN OF NUDE MICE

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In a recent study we investigated the effect of the co-administration of paclitaxel with the 2nd generation pgp-modulator valspodar on the intracerebral growth of human U118-MG glioblastoma. By this treatment the tumor burden was reduced by 90%. Now we studied the effect of the co-application of 3rd generation pgp-modulators elacridar and tariquidar, in vitro and in vivo. The results of the in vitro experiments (flow cytometry, calcine efflux, chemosensitivity) demonstrate that the new modulators are about 80 times more effective in comparison to valspodar (IC50: 24.2 nM for tariquidar, 20.3 nM for elacridar and 1.63 µM for valspodar). Nude mice received 50 mg/kg of valspodar, elacridar or tariquidar p.o. (control: vehicle) 4 h before i.v. injection of 8 mg/kg of paclitaxel. 1.5, 3, 4.5 and 24 h after paclitaxel application, plasma, brain, liver, and kidney were collected and analysed by means of RP-HPLC.

In liver and kidney the paclitaxel concentrations were similar in the control, the elacridar and the tariquidar group, whereas in the valspodar group the paclitaxel concentrations were significantly higher. In the plasma of valspodar treated mice the paclitaxel levels were 7.5 to 8 times higher than in the elacridar, tariquidar and control group. The paclitaxel levels of the control in the brain were close to the limit of quantitation. The paclitaxel concentrations in the brains of the valspodar group were 5 to 8 times higher than in the control group, whereas in the elacridar and tariquidar groups an only 4-fold increase compared to the control group was measured.

The brain/plasma ratio of paclitaxel in mice treated with elacridar or tariquidar indicates a more specific accumulation of paclitaxel in the brain. But compared to the effect of valspodar the resulting cytostatic levels in the brain are possibly too low for a therapy of glioblastoma.

HISTONE DEACETYLASE INHIBITORS AS POTENTIAL THERAPEUTIC AGENTS IN HIGH RISK NERVOUS SYSTEM TUMOURS OF CHILDHOOD - FIRST IN VITRO ANALYSES

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Introduction: Malignant tumors of the childhood CNS are poorly understood and certain risk groups remain difficult to treat. The epigenetic structure of DNA and its lesions contribute to the origin of these neoplasms. Manipulation of the epigenetic makeup offers opportunities for treatment.

Methods: We investigated whether histone deacetylase inhibitors (HDI) can stop the proliferation of tumor cells in vitro. 17 cell lines from medullo-blastomas (MB, n=5), neuroblastomas (NBL, n=6), primitive neuro-ectodermal tumors (n=2), and rhabdoid tumors of the CNS (n=2) and kidney (n=2) were tested. Standard MTT tests were used to evaluate the toxicity of nine HDI. Four cell lines (2NBL, 2MB) were further analysed by reexpression experiments. Each cell line was treated with four different substances (m344, MS-275, trichostatin A (TSA), and valproic acid).

Results: All substances tested showed inhibitory effects on cell growth. The GI50 concentrations after 72 hours ranging from 0.01 to 3.4 µM. Highest concentrations were necessary for valproic acid. The GI50 concentrations were significantly higher. In the plasma of valspodar treated mice the paclitaxel levels were significantly higher in the control group. Whereas in the elacridar and tariquidar groups an only 4-fold increase compared to the control group was measured.

The brain/plasma ratio of paclitaxel in mice treated with elacridar or tariquidar indicates a more specific accumulation of paclitaxel in the brain. But compared to the effect of valspodar the resulting cytostatic levels in the brain are possibly too low for a therapy of glioblastoma.

Supported by the Wasowicz- and the Karl-Bröcker-Stiftung.
PLATELET-DERIVED GROWTH FACTOR RECEPTOR INDEPENDENT PROLIFERATION OF HUMAN GliOBLASTOMA CELLS

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The aim of this study was to investigate the role of platelet derived growth factor (PDGF) and PDGF receptors (PDGFR) in the proliferation of human glioblastoma cells as a prerequisite for a new therapeutic approach to the treatment of malignant brain tumors with selective tyrosine kinase inhibitors such as Imatinib. In the human glioblastoma cell lines U-87 MG, U-118 MG and U-373 MG different PDGF and PDGFR mRNAs were detected by RT-PCR and the expression of the receptor proteins was demonstrated by immunostaining and flow cytometry. However, the addition of PDGF to the serum-free culture medium had no stimulatory effect on cell proliferation, even in serum-supplemented and serum-free medium cell growth was not affected by imatinib, lefunomide and AG-1296 at therapeutically relevant concentrations. Furthermore the sensitivity of the cells to PDGF was investigated by the ratiometric Fura-2 Calcium assay. Compared to Swiss 3T3 mouse fibroblasts almost no increase in the intracellular Ca²⁺ levels was observed. The PDGF-induced Ca²⁺ increase in the Swiss 3T3 cells was inhibited by an Imatinib concentration close to therapeutical levels (IC₅₀=4,16 µM).

In contrast to reports in the literature our results do not support the hypothesis that PDGFR receptor kinase inhibitors are effective new therapeutic agents in the treatment of malignant primary brain tumors.

TREATMENT OF MALIGNANT GLIOMAS IN VERY YOUNG CHILDREN (<3 year of age): RESULTS OF THE FIRST COOPERATIVE STUDY IN ITALY

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An analysis of all cases of malignant gliomas histologically proven of children <3 years of age enrolled in the first Cooperative Italian Study for Infants Malignant Brain Tumors, has been conducted in order to evaluate main clinical features and results of treatment aiming to identify peculiar features of this entity at this age and role of chemotherapy.

In the period 1995 – 2003, a total of 14 Malignant Gliomas were recruited, 7 males, 7 females; 7 (50%) were under 1 year of age; age ranged from 3 months to 36 months (median 18).

Treatment strategy in all cases was to remove as much as tumor possible when feasible and use chemotherapy as up-front modality in order to avoid or delay irradiation. RT was planned at the end of CT on residual tumor or at progression during chemotherapy. Chemotherapy protocols used were Standard Infants 8 cases (5 Baby SFOP, 3 SNC 95/1); Infants HR (including HD CT) in 6 cases; histology was GB 6 cases (2 giant cell variant); AA 3 cases; An. Oligodendrogliomas 2, other 3 (1 M. Gliomas not otherwise classifiable and presenting astroblastic features,2 malignant glio-epithelial tumors); site of involvement: hemispheres +/- basal nuclei infiltration: 11 cases (78.5%), Posterior Fossa (cerebellum-pontine angle) 1, Spinal Cord 1; Suprasellar 1.

Outcome: 5 (35.7%) patients are alive free of disease (ANED) at respectively 18, 52, 60, 68, 110 months from diagnosis; only 1 of them received RT after 5 years from dx for relapse at + 42 months form discontinuation of CT; 2 are alive with disease; 6 are died of tumor progression; 1 patient died in CR of unrelated causes.

Malignant Gliomas in infants tend to prevail at age <1 and in the supratentorial compartment. Cure is possible after treatment including chemotherapy only after surgery indicating a greater chemo sensibility comparing with older ages and also in grade GBL.

PEDIATRIC MALIGNANT GLIOMA OR PNET?: IMPLICATIONS FOR THERAPEUTIC MANAGEMENT: REPORT OF 2 CASES.

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We report 2 cases of unusual infantile malignant neuroectodermal tumors with morphological and immunohistochemical signs of gial differentiation.

In patient 1 a left temporal space-occupying lesion was diagnosed in the 28th gestational week. Prenatal MRI showed a paraventricular left temporal tumor. He was delivered in the 34th gestational week and operated 10 days after birth. Patient 2 is a 30-months-old male infant with an unremarkable development. Three weeks prior to the operation he had a rapidly progressive right-sided hemiparesis. MRI showed a paraventricular left fronto-centrally located tumor, clearly demarcated from the adjacent brain. In both patients a total tumor resection was performed.

Histopathology showed in both cases a cellular homogenous tumor tissue composed of relatively small cells with round isomorphic eccentrically located nuclei and a broad rounded eosinophilic cytoplasm, resembling small gemistocytic astrocytes.

Mitotic figures were frequently detectable, focally small areas of necrosis were present. Immunohistochemistry showed positive labelling of the tumor cells for gial markers. A small fraction of the cells expressed neurofilaments. No immunoactivity for synaptophysin, epithelial, or mesenchymal markers was detectable.

Both tumors were diagnosed as unusual infantile malignant gliomas being at the interface of glioma and PNET. The patients are treated according to a modified HIT-SKK 2000 protocol. Currently both patients do not show any evidence of tumor recurrence 3 and 12 months postoperatively.

We conclude that both tumors cannot be definitely classified according to the current WHO criteria. Postoperative adjuvant treatment (PNET versus malignant glioma protocol) requires interdisciplinary discussions in such cases.

VALPROIC ACID USED TO TREAT MALIGNANT GLIOMA IN CHILDREN

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We used the histone deacetylase inhibitor valproic acid (VPA) in the HIT-GBM-C protocol for the treatment of malignant glioma in children considering that glioma cells resemble immature glial cells, that can be prompted to either differentiate or to become apoptotic. Previously, we were able to show in preclinical studies that VPA changes the biology of neuroectodermal tumor cells towards differentiation, cytostasis, reduced metastatic capacity and increase of immunogenicity. Continuous oral intake of VPA after combined chemotherapy and irradiation for malignant glioma aimed at further reduction of tumor volume or at maintaining the previously achieved remission status ensuring quality of life. 53 children (32:21 m:f) were treated with VPA. 4 children were treated with VPA for epilepsy and 10 children achieved remission status ensuring quality of life. 53 children (32:21 m:f) were treated with VPA after combined chemotherapy and irradiation for malignant glioma.

Toxicity was negligible and patients with tumors responding to VPA treatment had an increased event-free survival. Thus, we consider that VPA should be further tested as an antiglioma drug.
TARGETING APOPTOSIS PATHWAYS FOR CANCER THERAPY OF MALIGNANT BRAIN TUMORS
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Most cancer therapies, e.g. chemotherapy, radiotherapy or immunotherapy, primarily act by triggering apoptosis, the cell’s intrinsic death program, in cancer cells. Thus, defects in apoptosis programs may lead to cancer resistance. We investigated the role of various signaling pathways in determining sensitivity or resistance of malignant brain tumors. Most glioblastoma cell lines exhibited constitutive activity of the PI3-kinase/Akt pathway. Importantly, inhibition of PI3-kinase activity markedly sensitized resistant glioblastoma cells to TRAIL- or cytoxic drug-induced apoptosis. In contrast, inhibition of MAPK or mTOR signaling had no effect on apoptosis sensitivity in these cells. Treatment with the mitochondriotropic cytotoxic agent Betulinic acid resulted in activation of NF-kappa B through activation of the IKK complex, phosphorylation and downregulation of IkappaB-alpha followed by translocation of the NF-kappa B subunit p65 into the nucleus and NF-kappa B-mediated transcriptional activation. Surprisingly, specific inhibition of NF-kappa B by expression of an IkappaB-alpha superpressor mutant, which suppressed NF-kappa B activation upon Betulinic acid treatment, also attenuated Betulinic acid-induced apoptosis pointing to a pro-apoptotic function of NF-kappa B in this context. Moreover, overexpression of mitochondrial or cytosolic Smac significantly increased irradiation-induced apoptosis of malignant glioma cells indicating that Smac agonists may be a useful tool to enhance radiosensitivity of malignant gliomas. Thus, understanding the molecular mechanisms that regulate cell death programs including apoptosis, and how resistant forms of malignant brain tumors evade apoptotic events, may provide novel opportunities for cancer drug development.

IMPROVED SURVIVAL AFTER GROSS TOTAL RESECTION OF PRIMARY AND RELAPSED MALIGNANT GLIOMAS IN PEDIATRIC PATIENTS
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The aim of the present study was to investigate the prognostic impact of tumor resection on survival in children and adolescents with primary and relapsed malignant gliomas. From the HHT-GBM databank (n=241) of the Society of Pediatric Oncology and Hematology (GPOH) in Germany, Austria, and Switzerland and from the Surveillance, Epidemiology, and End-Result (SEER) US database (n=18), 259 pediatric patients aged 0-18 years with histologically proven WHO grade III (n=106) and IV (n=153) non-pontine gliomas were analyzed. In 120 patients, additional data on second surgery after tumor relapse was available. The extent of tumor surgery during first-line treatment represented the most prognostic factor for overall (OS) and event-free survival (EFS) in univariate and Cox regression analysis. Five year survival after gross total tumor resection was 33.1±9.5% (OS) and 14.9±5.2% (EFS), after subtotal/partial resection 22.3±5.4% (OS) and 11.3±3.8% (EFS), after biopsy 13.2±6.3% (OS) and 0% (EFS). In Cox regression analysis, only histological grading showed a similar significance for OS and EFS whereas other clinical parameters either demonstrated significance only for OS (sex, tumor location) or no significance at all (radiotherapy, chemotherapy). In relapse patients, tumor reoperation appeared to represent an important part of a second-line treatment approach: Patients treated with second-line chemotherapy showed a significantly better 5 year OS with second gross total tumor resection (35.6±19.9%) than without additional tumor debulking (0%)). In conclusion, gross total tumor resection improves survival in pediatric patients with primary high-grade gliomas. A second-line treatment approach including tumor reoperation and chemotherapy appears advantageous for relapse patients.

SEQUENTIAL CHEMOTHERAPY, HIGH-DOSE THIOTEPA, CIRCULATING PROGENITOR CELL RESCUE, AND RADIOTHERAPY FOR CHILDHOOD HIGH-GRADE GLIOMA: A MONO-INSTITUTIONAL STUDY
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Background. Clinical behavior of childhood malignant gliomas is almost as aggressive as in adults, with resistance to therapy, rapid progression, and not uncommon dissemination. Methods. Our study protocol incorporated sequential chemotherapy and high-dose thiopeta in the preradiant phase, followed by focal radiotherapy and maintenance with vincristine and lomustine for a total duration of one year. The induction treatment consisted of two courses of cisplatin (30 mg/m²) plus etoposide (150 mg/m²) per 3 days, and of vincristine (1.4 mg/m²) plus cyclophosphamide (1.5 g/m²) plus high-dose methotrexate (8 g/m²), followed by high-dose thiopeta (300 mg/m² per 3 doses), with harvesting of peripheral blood progenitor cells (PBPCs) after the first cisplatin/etoposide course. Results. From August 1996 to March 2004, 24 children, 15 females and 9 males, with a median age of 10 years were enrolled, 21 presenting with residual disease after surgery. Histologies were glioblastoma multiforme in 12, anaplastic astrocytoma in 10, and anaplastic oligodendroglioma in 2; sites of origin were supratentorial areas in 19, spine in 3, and posterior fossa in 2. Of the 24 patients, 14 have died (11 after relapse, with a median time to progression for the whole series of 14 months; one for intratumoral bleeding at 40 months after diagnosis; one affected by Turcot syndrome for duodenal cancer relapse and one for pneumonia at 13 months after diagnosis). Four of 13 relapsed children had tumor dissemination. At a median follow-up of 48 months, over-all survival and progression-free survival at 4 years were 40% and 47%, respectively; PFS for pts with glioblastoma was 19% and for pts with other malignant glioma 75% (p=0.005), being OS 52% and 27% (p=0.06), respectively. Conclusions. Sequential and high-dose chemotherapy can be afforded in front-line therapy of childhood malignant glioma without excessive morbidity and rather satisfying results, especially in patients with anaplastic astrocytoma and oligodendroglioma.
RATIONALE AND METHODS: Conventional fractionation of radiotherapy (RT) of the tumor site alone yields a median survival of 12 months. Local dose escalations by using modern treatment techniques are promising. Conventional RT followed by radiosurgery in non-resectable tumors achieves survival times up to 72 months. After brachytherapy combined with conventional radiotherapy, tumor control rates of more than 80% at 4 years were observed. Reducing normal tissue volume included in the 95% isodose is a major aim to reduce the potential for late effects. Conformal radiotherapy in conjunction with modern functional imaging such as liposcopy and SPECT offers the possibility to include biological properties into treatment planning. In primary treatment and recurrent disease these tools provide delineation of high and low risk regions in order to achieve local adjustment of dose prescription.

Conclusions: Restricting the planning target volume by using conformal techniques appears to be feasible. The introduction of functional imaging may lead to a biological guided dose prescription. Local dose escalations by using modern techniques appear to improve local tumor control and warrant further investigation especially in incompletely resected high grade tumors. The use of modern treatment techniques achieves a reduction of normal tissue irradiation in order to reduce the potential for acute and long-term side effects. Generation of integral doses to target volumes and organs at risk allows the development of models to predict the risk of late effects.

Supported by Deutsche Kinderkrebsstiftung
MUTUAL CYTOKINE PRODUCTION BY IMMATURE DC CO-CULTURED WITH GliOBLASTOMA MULTIFORME TUMOR CELLS

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Glioblastoma Multiforme (GBM) is the most common primary central nervous system (CNS) neoplasm. Little is known about the interaction between GBM cells and antigen-presenting cells in the CNS. To mimic the micro-environment of the tumor, we co-cultured GBM cells with immature DC (DCi), which closely resemble microglia cells. DCi were generated in vitro by culture of adherent monocytes in the presence of rIL-4/rGM-CSF, after which they were co-cultured with GBM cells for 2 to 6 days. The production of IL-6, IL-10, IL-12, TNF-α and IFN-γ in the supernatant was measured with ELISA, and a stimulation index (co-culture compared to separate cultures) was calculated. DCi alone produced moderate amounts of IL-6. GBM cells alone produced IL-6 and in some experiments IL-12 (p70), the latter being confirmed also at the mRNA level. We found a significant induction of IL-6, IL-10, TNF-α and IFN-γ production in the co-cultures, which was totally dependent on direct cell-cell contact between tumor cells and DCi. DCi cultured in the presence of lysates of the GBM cells also produced IL-10, TNF-α and IFN-γ, but not IL-12. The data point to GBM cell-mediated stimulation of DCi resulting in the production of anti-tumoral factors (TNF-α, IFN-γ), but also tumor-promoting factors via angiogenesis (IL-6) and immune suppressive factors (IL-10), and possibly reflect the intratumoral micro-environment.

IMPROVEMENT OF DENDRITIC CELL VACCINATION STRATEGY FOR PATIENTS WITH RELAPSED HIGH GRADE GLIOMA: AN INTERIM ANALYSIS


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The results of the first cohort of the HGG-IMMUNO-2003 protocol show that immune response against high-grade glioma (HGG) can be induced by injecting autologous DC loaded with tumor proteins. With the schedule used, the induction of immunity takes about 2 months. CCR is obtained in several patients with complete tumor resection prior to vaccination. However, tumor control was sufficient for patients with residual disease. In order to induce immunization over a shorter time after resection, the next cohort of patients was scheduled for vaccinations each 2 weeks for V1 to V5, and later on each 4 weeks. When tumor resection was undoubtedly incomplete, patients were scheduled to receive in parallel weekly IV vinblastine (VBL) 6 mg/m², aimed to control tumor growth based on anti-angiogenesis during the period of immunization. Ten patients were treated thusfar (mean age: 41y; range: 19-60). One patient had immediate and massive relapse and received only one vaccination. Three patients are clearly progressive. Three other patients can be evaluated yet. One girl of 19y showed response of a lesion and is now in CCR. A boy of 22y had a complex history (Childs Nerv Syst 2004;20:114). He received vaccination, prepared out of one of 2 remaining tumors in the spinal axis, in combination with VBL. We demonstrated normal immunity against recall antigens in spite of VBL treatment. The residual tumor lesion remained stable for 6 months, and was removed afterwards. Because all material was used for further DC loading, pathology assessment of an immune response was not done. Three further vaccinations have been scheduled for him. Finally, a girl of 19 received also vaccination + VBL. She showed response of a small lesion and is now in CCR. We could perform skin test, and observed prominent delayed type hypersensitivity response. In general, there was no vaccination-related toxicity. Because of mild leukopenia, both VBL-treated patients had to reduce the dose to 4 mg/m². Although far too early to draw any conclusion, vaccination each 2 weeks is feasible. VBL seems not to counteract DC vaccination-based immunotherapy. Combining DC vaccination with 4 mg/m² VBL should be further investigated.

PALLIATIVE VALUE OF AGGRESSIVE TREATMENT IN HIGH GRADE GLIOMA AND DIFFUSE INTRINSIC PONTINE GLIOMA: PRELIMINARY RESULTS OF HIT-GBM-C

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Background: Despite significant efforts, most patients with diffuse intrinsic pontine glioma and high grade glioma die from their disease. A major debate continues, if the treatment with the inevitable toxicity is worth the benefit. For the individual patient, this benefit has three elements: The increased chance to survive, the temporary improvement of symptoms and signs, and the psychological effect of being cared for. In particular in diffuse intrinsic pontine glioma, the temporary improvement of neurological signs is retrospectively frequently valued very high by patents of deceased patients. But this is influenced by many factors and might not reflect the patients views. In order to add scientific data to this discussion, an attempt is ongoing to measure health related quality of life in the HIT-GBM- protocols.

Methods: Physicians participating in the HIT-GBM-C study were asked to fill in the FMH at various time points of the protocol. The FMH is a questionnaire to measure health related quality of life with simple objective questions focusing on the independence in daily life. 56 item are to be answered with Yes or No. The number of Yes answers is converted to a percent level using an age dependent percentile table (Klin Padiatrie, 208:294-8.1996).

Results: In the total HIT-GBM database, 161 patients (93 male, average age 10 years) were documented as treated with the HIT-GBM-C protocol between 1999 and 2003. The most frequent tumor locations were pons (58), cerebral cortex (59) and basal ganglia (18). WHO-grading was IV: 65; III: 55, the others were enrolled based upon the MRI morphology of diffuse intrinsic pontine glioma. The primary surgical resection was complete in 28, subtotal or partial in 58, with only biopsy or no surgery in the others. Only 88 patients received the simultaneous radiochemotherapy as prescribed in the protocol. FMH questionnaires were received from 49 patients (32 male, age 3-17, average 10.6 years). The diagnoses were: HGG WHO grade IV: 20; grade III: 17, diagnosis based upon MRI only: 12. The result of the resection was: complete 12, partial or subtotal: 13; biopsy or no surgery: 24. The average percentile FMH result from patients with German first language appeared higher (32±18.5 SD, n=43) when compared to others (17±9.9 n=6), but the difference was not statistically significant (p=0.1). When categorizing the first received questionnaire for each patient according the elements of the treatment protocol, the data came out as assumed: FMH percentiles were highest prior to the treatment: 53±21 SD, dropped after surgery and simultaneous radiochemotherapy to 29.7±18 SD, and continued on this level during chemotherapy consolidation (20.5±6) and valproic acid maintenance (24.9±11). At the time of recurrence the average FMH percentile was low (7.5±1.5). In 10 patients, more than one FMH questionnaire was received giving a very small basis to address the main question. Of those, 5 improved, 2 remained unchanged, and 3 deteriorated. Two of the three, which deteriorated had a tumor progression at that time, and one suffered from treatment side effects at the time of measurement. In the others the health related quality remained unchanged (2) or improved (5) despite aggressive treatment.

Conclusion: The improvement of health related quality of life during treatment of pediatric high grade glioma and diffuse intrinsic pontine glioma patients is measurable using the FMH. The data are too sparse to judge the treatment protocol HIT-GBM-C. We hope this report will encourage participation in the ongoing HIT-GBM-D protocol.
SUTURE AND ADJUVANT VACCINATION WITH TUMOR PROTEIN-LOADED AUTOLOGOUS DC FOR PATIENTS WITH RELAPSED MALIGNANT GLIOMA

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The survival of patients with relapsed malignant glioma is <12 months, in spite of a new surgical intervention. Immunotherapy using autologous mature DC loaded with autologous tumor homogenate was given to 23 relapsed patients with a median age of 30 y (6-78). In all patients fresh tumor tissue was obtained by repeat surgery. Vaccination started 4 weeks after surgery, and was repeated at week 1, 3, and further each 4 weeks. It consisted of intradermal injections of mature DC loaded with tumor lysate. Two patients were progressive immediately after surgery and were excluded for as-treated analysis. Complete (n=10, significantly younger patients), subtotal (n=7) and partial (n=6) response could be performed prior to vaccination. A median of 5 (3-7) vaccines was given. In the patient group with total resection, 4 patients are in continuous complete remission for 42, 41, 26 and 22 months (m). In the group with total tumor resection (n=10), the median progression-free survival (PFS) and overall survival (OS) was 13 respectively 23 m. In the 11 patients with residual tumor disease prior to vaccination, who developed repetitive vaccine-related peritumoral edema. Immunotherapy with autologous mature DC loaded with autologous tumor homogenate for patients with relapsed malignant brain tumors is feasible without major adverse events. The beneficial effect for improving PFS and OS by adjuvant tumor vaccination became obvious after complete resection of the relapsed tumor. DC vaccination should be discussed with respect to primary treatment.

EXTERNALLY APPLIED MONOCYTES INFILTRATE GLIOMA SPHEROIDS AND RAT GLIOMAS

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Objective: One prominent feature of gliomas is the lack of cellular anti-tumor immune response despite extensive infiltration with mononuclear cells. We established a model of monocytic invasion into glioma cell spheroids in vitro and showed that monocytes injected into the peripheral blood infiltrate rat gliomas in vivo.

Methods: Monocytes were isolated from human blood and added to precultured spheroids of U118 or A172 glioma cells. After three days, the spheroids were collected, fixed and examined immunohistochemically. Peritoneal macrophages were stained with the fluorescent marker PKH2, collected after 24h and injected into RG2-glioma-bearing Fisher rats intravenously or into the carotid artery. After 24h, the rats were sacrificed and frozen sections of the brains searched for fluorescent macrophages.

Results: Spheroids were infiltrated regularly by monocytes in vitro. The monocytes expressed MR8, MAC387 (MRP14) and 25F9. In the rat glioma model, accumulation of the marked monocytes in the tumor was observed 24h after injection into the peripheral blood.

Conclusions: The experimental models presented here allow to analyse interactions between monocytes and glioma cells both in vitro and in vivo. A better understanding of these interactions may help to overcome the inactivation of the monocytic anti-tumor response by glioma cells.

VALPROIC ACID AS A POTENT SUBSTANCE FOR INCREASING EFFICACY OF TOPOTECAN

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INTRODUCTION: Valproic acid was discovered as inhibitor of histone deacetylase, an enzyme for regulation gene expression for cellular proliferation and differentiation. It has been used as a treatment of tumor differentiation during the consolidation of the HIT-GBM-D protocol. There is some evidence that VPA could increase the efficacy of chemotherapeutics.

METHODS: U87MG, human glioma cells were plated with 3000 cells/well in 96 well plates. After 24 hours, VPA and topotecan were added. VPA was used in concentration of 100, 500 and 1000 µg/ml, topotecan was diluted 0.1 µg/ml to 8 µg/ml, with an incubation time of 72 and 120 hours. MTT-test was used for measuring cell viability. Cells were purchased from ATCC (USA), cell culture reagents from Sigma. Drugs were commercially available, licensed for patients' care.

RESULTS: VPA at concentration of 500 µg/ml induced cell proliferation 10% to 20%, 1000 µg/ml reduced proliferation 20%, 10% µg/ml had no effect on cell proliferation. Topotecan incubation was cytotoxic. The IC50 of topotecan was 0.8–1 µg/ml. Concentration below 0.01 µg/ml had no effect. Coincubation of topotecan and 100 µg/ml VPA for three days reduced cell proliferation 5–10% compared to incubation with topotecan alone. The same effect was seen with 500 µg/ml VPA: reduction of 20%. Incubation with 1000 µg/ml VPA over 72 h enhanced the reduction of cell viability: reduction of 40%. Increasing the incubation time to 120 hours, the effect was more enhanced: at a topotecan concentration of 1.25 µg/ml 100 µg/ml VPA reduced cell viability 40% compared to topotecan alone, 500 µg/ml VPA 76% and 1000 µg/ml VPA 100%.

CONCLUSION: A combination treatment of the histone deacetylase inhibitor VPA and topotecan, enhanced the antitumoral efficacy of topoisomerase I -inhibition.

PHASE II STUDY WITH PEGYLATED LIPOSOMAL DOXORUBICIN IN COMBINATION WITH ORAL TOPOTECAN CHILDREN WITH PROGRESSIVE HIGH-GRADE GLIOMA

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BACKGROUND: Synergism of a combination of topoisomerase I (topotecan) and II inhibitor (doxorubicin) was found in preclinical studies. Pegylated liposomal doxorubicin (Caelyx®) in opposite to free doxorubicin accumulates higher in tumor tissue than in normal tissue. A phase 1 study in children evaluated a dosage of 40 mg/m2 every 4 weeks as feasible. Good results were obtained in a study of HGG in adults with a dose of 20 mg/m2 every 2 weeks.

PATIENTS AND PROTOCOL: Topotecan was given orally 0.3 mg/m2 twice a day as a maintenance therapy. Caelyx® was individually adapted with a starting dose of 10 mg/m2 every 2 weeks over 6 weeks. In case of toxicity (NCI-CTC) <II, the dose was increased to 15 mg/m2 and than to the final dose of 20 mg/m2 every 2 weeks. Six patients were treated according to the protocol: an 11 years old girl with an anaplastic diffuse intrinsic pontine glioma (DIPG), an 11 years and a 10 years old boy with DIPG, a 12 years and a 10 years old boy with AA of the thalamus, a 10 years old girl with an anaplastic astrocytoma.

RESULTS: The patients received two (=1), 3 (n=2), 4 (n=1), 6 (n=1) or 11 (n=1) cycles of Caelyx®. Two patients were progressive immediately after surgery and were excluded too early for evaluating efficacy of the current protocol.

CONCLUSION: Toxicity of 20 mg/m2 every two weeks in combination with oral topotecan was tolerable. The protocol is still open for registration. It is too early for evaluating efficacy of the current protocol.
HIGH-DOSE METHOTREXATE IN CHILDREN WITH MALIGNANT HIGH-GRADE GLIOMAS

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BACKGROUND: Preradiation multiagent chemotherapy including methotrexate (MTX) was found to be effective in children with completely resected malignant high-grade gliomas (Wolff, Cancer 2004:264-71). Previous protocols of the prospective cohort comparison study HIT-GBM for children with malignant high-grade gliomas did not include MTX.

PATIENTS AND METHODS: Children with newly diagnosed, previously untreated high-grade malignant gliomas and diffuse intrinsic pontine gliomas (DIPG) were enrolled into the pilot-phase for the next HIT-GBM protocol. Two cycles of HD-MTX (5mg/m2over 24 h) were given on day 1 and 15 prior to simultaneous radiochemotherapy (SRCT), which was conducted as previously described (3). MRT was performed two weeks after completing SRCT. Statistical evaluations were done by means of the SPSS program.

RESULTS: 26 children, 17 males, age of 10.3 years (range 3.3-16.9 years) were enrolled. Resection was complete in 5 patients, subtotal in 5 patients, in 4 patients. Tumor grading was IV (n=9), WHO°III (n=10), II (n=3, DIPG). The toxicity of MTX was mild without grade IV toxicity. The toxicity after SRCT was: anemia °III 7/19, °IV 3/19, leukocytopenia °III 3/19, °IV 12/19, thrombocytopenia °III 4/19, °IV 8/19, infection °III 8/18, °IV 0/18. One patient experienced a subileus. There was no °III/IV inhepalatic, hepatic or dermal toxicity. Response was evaluated 3 weeks after irradiation. Stable disease or better was seen in 95.3%. (CCR: 2, CR: 1, PR: 8, SD: 5, PD: 1).

CONCLUSION: HD-MTX prior to simultaneous radiochemotherapy is well tolerated and feasible. Response data are encouraging. A randomized trial evaluating the effect of HD-MTX on survival is ongoing.

EFFECT OF ADDITIONAL VINCristine DURING SIMULTANEOUS RADIOCHEMOTHERAPY?

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BACKGROUND: Since 1995 the GPOH enrolls patients with malignant high-grade glioma and diffuse intrinsic pontine glioma in the prospective cohort comparison study HIT-GBM. This analysis compares early response and toxicity of induction chemotherapy according to the protocol and reference confirmation study HIT-GBM. This analysis compares early response and toxicity of induction chemotherapy according to the protocol and reference confirmation study HIT-GBM.

RESULTS: 129 patients (C-cohort: 66, B-cohort:56) were included in this analysis. Tumor grading of 11 cortical tumors, 2 cerebellar tumors, 9 pontine tumors, 6 ventricular tumors, 1 spinal and 1 thalamic tumor (unspecified n=3), was WHO°III (n=2; pontine tumors), WHO°III (n=13) and WHO°IV (n=13, unknown n=5). Resection was done in 19 tumors, 7 completely. Chemotherapy was given to 22 children (HIT-SKK:14, HIT-GBM:5, other:3, no:8, unknown:3. 10 patients were irradiated after chemotherapy, median dose 54 Gy. 7 children were treated with intracathelic methotrexate. For the total group, 2 year OS was 47±6%. Survival longer than five years was seen in 39% of the children. There is no significant difference in OS between children with and without pontine tumors, between males and females. Significant better OS was analyzed in WHO°III tumors compared to °IV tumors (p=0.0347), and in age older than 4 months (p=0.0004). Significant better OS was seen in resected tumors (complete resection was not important, p=0.0008), and in children treated with chemotherapy (p=0.0005).

CONCLUSION: High-grade gliomas in infants and very young children have a different biological behaviour than tumors in older children. They are highly chemosensitive and despite the lack of irradiation, they have a better prognosis. Within this group the subgroup of neonatal tumors has to be observed separately.
combined treatment of pediatric high-grade glioma with the oncolytic viral strain mth-68/h and oral valproic acid

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BACKGROUND: Valproic acid is recently discovered as a histone deacetylase inhibitor and known as a drug with proven differentiation potential. MTH-68/H, an attenuated strain of the New Castle Disease Virus, an oncolytic virus replication competent virus which replicates specifically in the tumor tissue by destroying the tumor cells.

CASE REPORT: A 12-year-old boy with anaplastic astrocytoma of the left thalamus was registered into the HIT-GBM-C study. Postoperative simultaneous irradiation and chemotherapy according to the protocol did not repress progression. Therefore, treatment was undertaken with valproic acid (VPA) and an attenuated strain of Newcastle disease virus (NDV) MTH-68/H. This treatment resulted in tumor regression of the thalamic glioma lasted for four months. Four months later, a new tumor manifestation, an extension of the thalamic tumor, appeared in the wall of the IVth ventricle and required a second neurosurgical intervention. Under continuous MTH-68/H – VPA administration the thalamic tumor remained under control, but the rhombencephalic one progressed irresistibly and led to the fatal outcome. The comparative histological study of the two tumor manifestations revealed that MTH-68/H treatment induces, a massive apoptotic tumor cell decline.

CONCLUSION: Valproic acid in combination with vaccination of MTH-68/H, an attenuated strain of the oncolytic New Castle Disease Virus, in a boy with progressive anaplastic glioma led to an unexpected rapid and extensive tumor regression. Mechanisms leading to these results have to be evaluated in further studies.

Polish/German Data base: Age and sex related outcome of malignant High-grade gliomas

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Background: The incidence of pediatric malignant high-grade gliomas is very low, only about 4% of all brain tumors. To perform clinical prospective or retrospective studies, it might be necessary to cooperate internationally. Therefore, we initiated a German/Polish cooperation.

Patients and Methods: The German/Polish data base enrolled patients with newly diagnosed malignant high-grade gliomas and pontine gliomas. The Polish data were collected from 1982 to 2003 at the Children’s Memorial Health Institute, the German data from 1983-2003 in the German speaking region. Different treatment schedules were used in both data bases. We analyzed the data concerning relation of sex and age with overall survival by Kaplan Meier curves and log-rank test using the SPSS®-statistical program.

Results: In total 551 patients (99 of the Polish and 453 of German data base, 299 males and 356 females) were included in this analysis. The mean age was 9.7 years (range 0.01 - 21.3 years). 117 tumors were totally resected, 69 subsaltently, 96 partially and 249 were not resected. Grading was found to be I° (n= 5), II° (n = 23), III° (n = 222) and IV° (n = 213 ). In the Polish data more III-tumors compared to the German data (61.6% versus 35.5%, chi-square p=0.005) and more totally and subtotally resected tumors (59.6% versus 28.2%, chi-square p=0.005) were found.

There is no difference in the distribution of gender and age between the two data bases. Evaluating the gender differences in overall survival (OS), females have a significant better five-year overall survival (5YOS, 28.8% ± 3.5%) than males (15.9% ± 2.8%, p=0.0064). In subgroup evaluation the 5YOS of females with grade III tumors (n=83, 46.7% ± 6.4) was significantly better than in males (n=29, 4.5% ± 5.8, p=0.0076), whereas in IV° gliomas, the difference of OS was not statistically different (5YOS of females: 32.5%±6.2, n=85; males 13.8% ± 4.3, n=101; n.s.). Evaluating the OS in different age groups of the entire data base, no survival advantage for younger or older patients was found.

Conclusion: These are the first results of a European cooperation in joining the Polish and the German data bases. The survival advantage of females caused probably by hormonal or even genetic circumstances has to be evaluated in further studies. The differences in the two data bases will be elucidated by comparing histlogy, criteria of amount of resection and the practice of surgery.


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Introduction: Quite frequently, the intraoperative view of possible residual tumor differs from the assessment of the postoperative MRI. On the one hand, when the MRI is done too late, the posttraumatic angiogenesis might mimic tumor. On the other hand, a microscopically visible sheet of tumor cells might be seen by the neurosurgeon but not by the MRI.

Methods: Choroid Plexus tumors (CPT) are extremely rare. Therefore, in 2000 we started an international registry for all CPT and randomized trial for those who need postoperative treatment. The treatment protocol contains maximal possible surgery, postoperative chemotherapy for all patients, 6 weeks delayed irradiation for those who are 3 years or older, and further chemotherapy for all. A total of 6 blocks of chemotherapy with VP16 100 mg/m2, x 5 days, and VCR 1.5 mg/m2 x1, and either carboplatinum 350 mg/m2 x2d (arm CarbEV) or cyclophosphamide 1g/m2 x2d (arm CycEV).

Results: In total 63 patients were registered from 14 nations: age 0-45 years median 1.8 years, 34 male, 24 choroid plexus carcinoma (CPC), 14 atypical choroid plexus papilloma (APP), 25 choroid plexus papilloma (CPP). Primary metastases were frequent: 4/20 CPC, 4/12 APP, and 1/13 CPP. The cumulative over all survival at 2 years was 78 ± 13 %. Histology was a significant prognostic factor with only one death in the group of CPP or APP. Among CPC patients, infratentorial location was linked to poor prognosis (p=0.05 log rank). Within the group of CPC irradiation was linked to better overall survival (p=0.05). The neurosurgeons report and the MRI agreed in 29 complete resections, and 7 partial resections. In 5 CPC patients the neurosurgeon reported complete resections, but the MRI not. In 3 cases it was the other way around. When looking at overall survival and separating the groups by the MRI result, patients with completely resected tumors had a better prognosis, but the difference to the other groups was not statistically significant (3YOS 83% versus 62% n.s.). When using the neurological reports, patients with either biopsy or partial resection had better overall survival than those with “complete resection” (p<0.008).

Conclusion: When CPC patients receive intensive nonsurgical treatment, the role of surgery appears to be less prominent than previously assumed. For the purpose of an international trial, the postoperative MRI is more reliable than the neurological report.
CHEMOTHERAPY IMPROVES THE PROGNOSIS OF CHOROID PLEXUS CARCINOMA

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Introduction: The question, if chemotherapy of choroid plexus tumors (CPT) improves the prognosis has frequently been discussed. An international study comparing two chemotherapy arms is on its way, but a study comparing no treatment to chemotherapy will probably never be done.

Methods: In 1998, a database had been created summarizing all published cases until 1997. A comprehensive evaluation of risk factors had been based upon this (Br J Cancer 2002 87:1086-91), the most frequently debated single finding was the benefit of irradiation to patients with completely resected choroid plexus carcinoma (Lancet,1999 353:2126). Now, this analysis was validated, by repeating the previous work with an independent new reader and comparing to the old database. New cases published until 2004 were added.

Results: 857 cases were documented. (male: female = 1.22:1, age at diagnosis: 0-73 median 3years). 347 had choroid plexus carcinoma (CPC), 15 atypical choroid plexus papilloma (APP), and 495 choroid plexus papilloma (CPP). The 5, 10 and 20 year overall survival rate of all patients was 64%, 51%, and 42% with no plateau in the survival curve. Histology was a significant prognostic factor (p<0.0001 log rank). Within the subgroup of CPC, both irradiation and surgery were still linked to a better prognosis in the new larger database (p<0.005). 82 CPC patients received chemotherapy of various protocols and had a statistically better survival when compared to those without chemotherapy (p<0.0008). When this was repeated in subgroup analyses, the statistical significance disappeared in the group of completely resected CPC, but it remained significant in the subgroup of less than completely resected CPC (2YOS 54.8% ± 7SD versus 24.4 ± 7, p<0.001). In further subgroups, the number became small, and we could not show a benefit from chemotherapy among patients with completely resected CPC. But the benefit of chemotherapy remained statistically significant among partially resected CPC with postoperative irradiation, among partially resected CPC without postoperative irradiation.

Conclusion: Chemotherapy should be given to patients with less than completely resected choroid plexus carcinoma regardless if they received irradiation. It remains unclear, if one of the two postoperative treatment modalities is sufficient to treat completely resected CPC.

IRRADIATION IMPROVES THE PROGNOSIS OF CHOROID PLEXUS CARCINOMA

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Introduction: The question, if irradiation of choroid plexus tumors (CPT) improves the prognosis has frequently been discussed. Most of the patients are too young for irradiation. For patients of 3 years and older, the prospective randomized study CPT-SIOP-2000 recommends irradiation.

Methods: In 1998, a database had been created summarizing all published cases until 1997. A comprehensive evaluation of risk factors had been based upon this (Br J Cancer 2002 87:1086-91), the most frequently debated single finding was the benefit of irradiation to patients with completely resected choroid plexus carcinoma (Lancet,1999 353:2126). Now, this analysis was validated, by repeating the previous work with an independent new reader and comparing to the old database. New cases published since 1997 were added.

Results: 857 cases were documented. (male: female = 1.22:1, age at diagnosis: 0-73 median 3years). 347 had choroid plexus carcinoma (CPC), 15 atypical choroid plexus papilloma (APP), and 495 choroid plexus papilloma (CPP). The 5, 10 and 20 year overall survival rate of all patients was 64%, 51%, and 42% with no plateau in the survival curve. Histology was a significant prognostic factor (p<0.0001 log rank). Within the subgroup of CPC, irradiation was linked to a better prognosis (p<0.002). This remained true in further subgroup analyses: 32 of 92 completely resected CPC had irradiation, and a better survival when compared to the not irradiated tumors (5OS 76.9% ± 8SD versus 46.3% ± 8SD, p<0.01). 44 of 109 incompletely resected CPC had irradiation and a better prognosis than those not irradiated (5YOS 54 ± 8 vs. 32.9 ± 6, p <0.009). The difference was still statistically significant, when looking only at those CPC, which were completely resected and had no chemotherapy. Among the group of completely resected CPC with chemotherapy, the trend remained the same, but the numbers became too small for statistical significance.

Conclusion: Irradiation should be given to patients with choroid plexus carcinoma, which are over 3 years of age. It remains unclear, if chemotherapy can substitute for irradiation after complete resection.