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Phase I clinical trial with BNCT for patients with glioblastoma (EORTC Protocol 11961)

W. Sauerwein, K. Hideghéty, R. Moss, C. Goetz, P. Pacquis, J. Rassow, F. Grochulla, K. Haselsberger, J. Wolbers, B. Turowski, H. Fankhauser, F. Stecher-Rasmussen, M. de Vries, D. Gabel. *EORTC BNCT Study Group; Strahlenklinik, D-45122 Essen, Germany*

Purpose: Boron neutron capture therapy (BNCT) is based on the high cross section of ^{10}B to capture thermal neutrons leading to the reaction $^{10}B(n, \alpha)^{7}Li$. In a phase I trial the radiation dose is escalated to investigate the healthy tissue tolerance of BNCT using the drug BSH and an epithermal beam at the European High Flux Reactor in Petten (NL).

Methods: BNCT was performed postoperatively in 4 fractions in patients suffering from glioblastoma. The systemic toxicity of BSH, the early radiation and late radiation toxicity were evaluated.

Results: Up to date the treatment of the first cohort of 10 patients has been evaluated. One transient grade 4 leucopenia possibly due to BSH, tolerable acute radiation toxicity (skin erythema, focal hair loss, headache) and one probably treatment related serious late radiation toxicity (cerebral infarction) were detected. The trial is being continued at the scheduled 10% higher dose level.

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Enhanced expression of drug-resistance protein LRP in astrocytic brain tumor cells

S. Spiegl-Kreinecker[1], J. Buchroithner[2], J. Fischer[2], M. Micksche[1], W. Berger[1]. *[1]Inst. of Cancer Research, Applied and Experimental Oncology, Vienna; [2]LNK Wagner-Jauregg, Neurosurgery, Linz, Austria*

Purpose: Lung resistance-associated protein (LRP), considered to be the human major vault protein, may play a role in drug resistance by regulating vesicular and nucleocytoplasmic transport processes. In order to assess the role of LRP in brain tumors, the expression of this protein was investigated in brain tumor cell lines (astrocytic N = 13; non astrocytic: medulloblastoma N = 2, neuroblastoma N = 4) and primary cultures from human glioblastoma multiforme (GB, N = 14).

Methods: LRP expression was studied by means of RT-PCR and immunfluorescence staining (monoclonal antibody LRP-56).

Results: LRP gene expression at the mRNA level was detectable by RT-PCR in 100% of the studied cell lines and primary cultures. High expression levels were detected in all primary cultures of GB, and only 1/13 astrocytic tumor cell line expressed low levels of LRP mRNA. All cell lines derived from non-astrocytic brain tumors expressed detectable LRP mRNA but at a significantly lower level as compared to the asctrocytic ones. Immunostaining for LRP correlated with RT-PCR data. Whereas in most of the primary cultures 100% of the cells scored positively for LRP, different cell subpopulations were evident in astrocytic tumor-derived cell lines. One subpopulation displayed vesicular LRP-reactivity in the cytoplasm, a second one still a vesicular staining pattern but associated to the outer side of the cell membrane. A third subpopulation (from 5 up to 80%) lacked LRP reactivity. In mitotic cells, homogeneously dispersed small vesicles all over the total cytoplasm displayed LRP-reactivity. In all non-astrocytic tumor-derived cell lines no or only very low LRP-immunostaining was detectable.

Conclusion: A high LRP expression seems to be a characteristic of malignant astrocytic cells. The differences between primary cultures and cell lines suggests that expression might be reduced during in vitro cell culture. Further studies are needed to clarify the impact of LRP on drug sensitivity in brain tumors.

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Supratentorial low-grade glioma: Results and prognostic factors following postoperative radiotherapy

G.G. Grabenbauer[1], C.M. Roedel[1], W. Paulus[2], R. Fahlbusch[3], R. Sauer[1]. *[1]Dept. of Radiation Oncology; [2]Pathology; [3]Neurosurgery, University Hospitals of Erlangen, Germany*

Background: To assess treatment outcome and prognostic factors following postperative external radiotherapy (RT) in 77 patients (pts) with low-grade glioma.

Material and methods: Between 1977 and 1996, 45 pts with astrocytoma, 14 with oligodenroglioma and 18 with mixed glioma received postoperative RT with a median total dose 52 Gy (range 40–61 Gy). Sixty-seven pts were treated immedialety following surgery, ten pts with tumor progression. The influence of various factors (histology, gender, age, seizures, duration of symptoms (≤6 weeks vs. >6 weeks), CT pattern (enhancement vs. no enhancement), type of surgery, total RT dose, timing of RT, proliferation and apoptosis) on relapse-free survival and overall survival was investigated.

Results: The median overall survival time was 81 months, while the 5- and 10-year-overal survival (OS) rates were 54% and 31%, respectively. The median time to progression was 56 months, while the 5- and 10-year-progression-free survival (PFS) rates were 45% and 24%. Univariate analyses identified the total RT-dose (p = 0.01), duration of symptoms (p = 0.05), seizures (p = 0.04), patients age (p = 0.03) and the CT pattern (p = 0.005) as significant prognostic factors for OS. PFS rates were influenced by the identical factors. On multivariate analysis, only the age at diagnosis and the CT pattern remaind independent prognostic factors for both PFS and OS.

Conclusion: A minimum total dose of 52 Gy is recommended for the postoperative RT in low-grade glioma. Tumors with CT enhancement seem to need further intensification of treatment.

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A brain cancer clinical assessment tool (BC CAT) for monitoring disease status in high-grade gliomas

D. Osoba[1], B. Zee[2], M. Brada[3], W.K.A. Yung[4], C.S.W. Weng[5], D. MacDonald. *[1]QOL Consulting, Vancouver; [2]Clinical Trials Group, National Cancer Institute of Canada, Kingston, Canada; [3]Institute of Cancer Research and Royal Marsden NHS Trust, Sutton, United Kingdom; [4]MD Anderson Cancer Center, Houston; [5]Schering-Plough Co., Kenilworth, Canada*

Purpose: To develop a practical clinical tool for monitoring the clinical progress of patients with glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA) who are at high risk for progression of disease.

Methods: A recursive partitioning method was applied to data from health-related quality of life assessments (EORTC QLQ-C30 plus Brain Cancer Module 20) and neurological examination obtained in 364 patients (pts) with recurrent GBM and 163 pts with recurrent AA. The data came from 3 studies involving the use of a new chemotherapy agent (temozolomide), in which HRQL data was obtained every 4 wk and enhanced MRI/CT scan data was obtained every 8 wk. The data was used to construct a clinical decision tool applicable in practice.

Results: For pts with GBM, a simple tool with 3 variables (speech, appetite, physical functioning) had a specificity (true negative rate) of 87% and sensitivity (true positive rate) of 34%. In AA, a tool with 2 variables (role functioning, neurological motor status) has a specificity of 90% and a sensitivity of 33%.

Conclusion: A BC CAT composed of HRQL and neurological examination data has high specificity (accuracy in diagnosing nonprogression), but its low sensitivity (accuracy in predicting progressive disease) requires further work.

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Comparison of radiotherapy dose distribution and FDG-PET after irradiation in patients with malignant glioma

F. Paulsen, M. Müller-Berg[1], G. Becker, M. Reimold[1], P. Hipp[1], T. Hehr, M. Buchgeister[2], W. Müller-Schauenburg[1], R. Bares[1], M. Bamberg. *Depts. Radiother., [1]Nuclear Med.; [2]Med. Phys., University of Tübingen, Germany*

Purpose: Despite multidisciplinary therapeutic approaches local relapses are often seen in patients with malignant gliomas. Informations derived from positron emission tomography (PET) are seldom taken in account for treatment planning in radiotherapy (RT) or follow-up. We correlated dose distribution of radiotherapy and posttherapeutic FDG-PET-imaging.

Patients and methods: 11 patients with malignant gliomas (glioblastoma (n = 6), mixed glioma III° (1), oligodendroglioma II° (1) and III° (1), astrocytoma II° (1) and III° (1)) were examined in suspicion of recurrence with FDG-PET 3–14 months after radiotherapy (54–60 Gy). In 1 patient with in-field-relapse after RT (60 Gy) a second irradiation with 20 Gy was performed before PET. FDG-PET activity was compared with dose distribution in treatment planning-CT.

Results: In 10/11 cases hypermetabolic areas were found: 4 in the RT-target volume (3 histologically proven (pr) recurrences), 4 at the field edge in the central beam (1 pr non malignant reaction, 2 pr recurrence), 1 at the caudal field edge (pr recurrence), in the patient with re-RT at the caudal field edge of the re-RT-field (pr recurrence). The lesions had different levels of (hyper-)metabolic activity in comparison to the gray matter.