randomised into four groups with 7 animals in each group. One group was untreated. A second group received ZD6474 30 mg/kg daily as an oral gavage for 14 days, starting day 6 after tumour implantation. A third group received temozolomide 100 mg/kg for three days, day 9, 12 and 15 after tumour implantation. The fourth group was treated with both ZD6474 30 mg/kg and temozolomide as mentioned above. Animals were sacrificed on day 20 and tumour size was measured.
Results: ZD6474 30 mg/kg in combination with temozolomide significantly decreased median tumour area from 13 mm^2 (range 8–14) in untreated controls to 3 mm^2 (range 0–8) ($p = 0.003$) in the combination group.
Conclusions: The orally available VEGFR2/EGFR tyrosine kinase inhibitor ZD6474, reduced tumour growth in an intracerebral rat glioma model. Combination with temozolomide results in more than additive effects. These results reported justify further investigations on the combined effects of ZD6474 and temozolomide in malignant glioma.

488 ORAL

Different angiogenic phenotypes in primary and secondary glioblastomas

C. Herold-Mende[1], S. Karcher[1], H. Steiner[1], R. Ahmadi[1], G. Vasvari[2], A. Unterberg[1]. [1]*University of Heidelberg, Neurosurgery, Heidelberg, Germany;* [2]*University of Heidelberg, ENT-Department, Heidelberg, Germany*

Primary and secondary glioblastomas (pGBM, sGBM) are supposed to evolve through different genetic pathways including EGF receptor and PDGF and its receptor and thus genes that are involved in tumor-induced angiogenesis. However, whether other angiogenic cytokines are also differentially expressed in these glioblastoma subtypes is not known so far but this knowledge might be important to optimize an antiangiogenic therapy. Therefore we studied the expression of several angiogenic cytokines including VEGF, HGF, bFGF, PDGF-AB, PDGF-BB, G-CSF and GM-CSF in pGBMs and sGBMs as well as in gliomas WHO III the precursor lesions of sGBMs.
In tumor tissues expression of all cytokines was observed albeit with marked differences concerning intensity and distribution pattern. Quantification of the cytokines in the supernatant of 30 tissue-corresponding glioma cultures revealed a predominant expression of VEGF in pGBMs and significantly higher expression levels of PDGF-AB in sGBMs. HGF and bFGF were determined in nearly all tumor cultures but with no GBM subtype or malignancy-related differences. Interestingly, GM-CSF and especially G-CSF were produced less frequently by tumor cells. However, GM-CSF secretion occurred together with an increased number of simultaneously secreted cytokines and correlated with a worse patient prognosis and may thus represent a more aggressive angiogenic phenotype. Finally, we confirmed an independent contribution of each tumor-derived cytokine analyzed to tumor-induced vascularization.
Our data indicate that an optimal antiangiogenic therapy may require targeting of multiple angiogenic pathways that seem to differ markedly in pGBMs and sGBMs.

Poster presentations (Mon, 31 Oct)
Central nervous system

489 POSTER

Fractionated stereotactic radiotherapy for vestibular schwannoma: single institutional experience at the Princess Margaret Hospital, Canada

E. Koh, B.-A. Millar, C. Menard, H. Michaels, M. Heydarian, S. Ladak, S. Mckinnon, N. Laperriere. *University of Toronto, Dept. of Radiation Oncology, Toronto, Canada*

Objectives: To assess the effectiveness of stereotactic fractionated radiation therapy (SFRT) in achieving local tumour control and hearing preservation in vetsibular schwannoma (VS). To document symptom presentation, and acute and long term treatment-related toxicities.
Methods: Retrospective review of 66 consecutive patients treated from October 1996 to February 2005. Five patients were excluded, two NF-2 associated, two discontinued at 28 and 30 Gy, and one received single fraction radiosurgery (15.5 Gy to the 90% isodose.)
Results: 61 patients were analyzed, 32 males and 29 females, age range 18–80 years (median 58). Median primary tumor volume was 4.9 cc (0.3–49). At presentation, imaging progression occurred in 28 (45.9%) and symptom progression in 8 (13.1%). Presenting symptoms included tinnitus (52.5%), gait instability (49.2%), CNV numbness (32.8%), facial nerve weakness (13.1%), and trigeminal neuralgia (4.9%). 95.1% had some degree of hearing loss and 24/61 (39.3%) had useful hearing at baseline. Formal baseline audiology was documented in 76%. Sixty patients received 50 Gy in 25 fractions, one received 52 Gy. Acute toxicities included grade I fatigue (43%), nausea (41%), grade I headache (20%), and occasional vomiting (5%). Grade II toxicities occurred in 5%. Most pre-existing cranial nerve V and VII dysfunction remained stable. No new cranial nerve palsies developed. One case of RT-induced Glioblastoma multiforme occurred 5.8 years post therapy. At a median follow up of 23.4 months, actuarial progression free survival was 98%. One patient experienced tumour progression at 2.3 months post-RT and underwent resection. Hearing function remained stable in 77% for all patients, in 82% and 67% with baseline useful and non-useful hearing. 6% noted improvement if initial hearing was useful.
Conclusion: FSRT for VS prescribed to 50 Gy in 25 fractions over five weeks is well tolerated. An excellent crude local control rate of 98.3% is achieved which is comparable to the published literature.

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Phase II/III randomized study of edotecarin vs. temozolomide or nitrosourea in patients with recurrent glioblastoma (GBM): Phase II results

M. Gilbert[1], M. Campone[2], A.A. Brandes[3], S. Gertler[4], S. Green[5], C. Fowst[6], J. Caulkins[5], A. Ingrosso[6], M. Foley[5]. [1]*MD Anderson Cancer Centre, Neuro-Oncology, Huston, USA;* [2]*Centre Renè Gauducheau, Oncologie Médicale, Nantes Saint Herblain cedex, France;* [3]*Azienda Ospedaliera di Padova, Medical Oncology, Padova, Italy;* [4]*Ottawa Hospital The Ottawa Hospital – General Campus, Regional Cancer Centre, Ottawa, Canada;* [5]*Pfizer Inc., Clinical Research Oncology, New London, USA;* [6]*Pfizer Inc., Clinical Research Oncology, Milan, Italy*

Background: Recurrent GBM has a very poor prognosis. Despite the use of systemic chemotherapy, the median survival time after tumor recurrence is less than 6 months. Edotecarin (Edo), a novel inhibitor of topoisomerase I that showed activity in brain tumor models and a good safety profile in Phase I studies, was tested in this population in a large multinational Phase II/ III trial.
Methods: Eligible patients (pts) had histologically proven GBM at first relapse after initial surgical tumor debulking or biopsy, external beam radiotherapy and temozolomide (TMZ) – or nitrosurea-based adjuvant chemotherapy. Other eligibility criteria included Karnofsky performance status (KPS) $\geqslant 70$, age $\geqslant 18$, and measurable disease confirmed by Gd-MRI. Pts were randomized 2:1 to Edo (13 mg/m^2/q3w, IV) or control (TMZ, BCNU or CCNU at standard doses). Target sample size was 525 pts. Randomization was stratified by age, KPS, and prior chemotherapy. The primary objective was to demonstrate an overall survival (OS) advantage for Edo over the control arm. The trial was powered to detect a 33.3% improvement (from 6 to 8 month median). The trial design included an interim Phase II analysis, which was based on the first 50 response-evaluable (measurable disease and treated) pts randomized to Edo. The criterion for trial continuation was 3 confirmed objective responses by MRI using the MacDonald criteria as determined by independent central radiology review.
Results: From July 2003 to August 2004, 50 centers randomized a total of 118 pts, 79 to Edo and 39 to control. Pt characteristics were well balanced by treatment arm; 70% had prior TMZ, 43% had KPS $\geqslant 90$, 40% had age $\leqslant 50$. Although numerous eligibility issues were retrospectively identified, no confirmed responses were observed in the first 50 response-evaluable Edo patients or in any of the 118 pts. Estimated median OS is 6.5 for the 79 Edo pts and 6.6 months for the 39 controls. Toxicity profile was acceptable. The study was closed to enrollment due to the poor response rate.
Conclusions: This was the first randomized, multinational trial in pts with recurrent GBM after surgery and chemoradiation. Results demonstrated insufficient activity in the Edo arm to continue the trial.

491 POSTER

Radiotherapy for pituitary adenomas: a twenty-year cohort

D.S. Conkey[2], A. Gregor[2], G.R. Kerr[2], P. Statham[3], M. Strachan[4], S. Erridge[1,2]. [1]*University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom;* [2]*Edinburgh Cancer Centre, Western General Hospital, Edinburgh, United Kingdom;* [3]*Department of Neurosurgery, Western General Hospital, Edinburgh, United Kingdom;* [4]*Department of Endocrinology, Western General Hospital, Edinburgh, United Kingdom*

Background: Radiotherapy (RT) has proven effective in the management of pituitary adenomas. However, control rates decline and toxicity increases with prolonged follow-up. The aim of this retrospective study was to determine the long-term control rate and toxicity in a large series of patients from a single centre.