Conclusions: Yet, the current standard of care seems to remain craniospinal irradiation after maximal surgical resection of the primary neoplasm without clear indications for adjuvant chemotherapy.

501 POSTER

Imatinib plus hydroxyurea: safety and efficacy in pre-treated, progressive glioblastoma multiforme (GBM) patients (pts) – an update on the initial 30 pts

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Background: GBM is one of the most aggressive malignancies with a median survival of about 1 year. In newly diagnosed GBM combined treatment including surgery and chemo-/radiotherapy leads to 2 years progression free survival (PFS) of 11% and 2 years overall survival of 26%. The prognosis is even worse in pts with recurrent GBM. Many malignancies of the brain including GBM express platelet derived growth factor receptors (PDGF-R). Imatinib, a tyrosine kinase inhibitor of Bcr-Abl, PDGF-Rs and the Kit receptor, showed remarkable clinical efficacy in chronic myeloid leukaemia and gastrointestinal stromal tumours. In GBM, however, single agent efficacy was probably limited due to the blood brain barrier (BBB). Therefore Hydroxyurea (HU) which freely penetrates and potentially modulates the BBB was combined with imatinib to study if efficacy could be improved.
Methods: From June 2001 to September 2003 30 GBM pts refractory to radiation therapy and chemotherapy containing ACNU and temozolomide were treated with imatinib 400 mg/day and HU 1000 mg/day as continuous daily, oral dosing, followed by clinical examination and magnetic resonance imaging every 6 weeks.
Results: All 30 pts are evaluable for safety and efficacy. Initial ECOG-performance status was 1–2, the median age was 44 yrs (16–71). Results after a median treatment period of 19 weeks (4–145) were one complete response (CR) lasting 12 months, 4 partial responses (PR) lasting a median of 3 months (3–29), 11 stable diseases (SD) for a median of 6 months (3–33) and 13 progressive disease (PD). There were no grade 3 or 4 toxicities. 27 deaths occurred: 2 pts died of pulmonary embolism and 25 pts of disease progression, 2 pts after a period of SD of 25 and 34 months. 3 pts remain alive, 2 pts without progression for 32 and 28 months respectively, 1 pt had a disease progression after 26 months of SD and is in another period of SD since 4 months with the combination chemotherapy temozolomide plus pegylated liposomal doxorubicin. Six months PFS was 32%, 2 years PFS was 16%.
Conclusions: Combination therapy of imatinib and HU was well tolerated and effective in this group of recurrent, refractory GBM pts, with a response rate of 20% (CR+PR) and a clinical benefit rate of 57% (including SD), 2 years PFS was 13%. Based on these results, additional studies have been initiated to further explore this regimen.

502 POSTER

Imatinib plus Hydroxyurea in Pretreated Non-Progressive Glioblastoma (GBM) – a Single Center Phase II Study

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Introduction: GBM is a platelet derived growth factor receptor (PDGF-R) positive malignant brain tumor with a median survival of less than 15 months. While single agent Imatinib (I) did not show significant activity the combination of I plus Hydroxyurea (HU) could demonstrate efficacy in a group of 30 progressive pretreated GBM patients with progression free survival at 6 months and 24 months of and 16% respectively. 37% of the patients eperienced a stable disease (SD) as best response with longterm stabilisation for more than 2 years being possible. GBM although one of the most aggressive solid tumors usually shows a short period of disease stabilisation after primary treatment or effective treatment of the first relapse. Therefore the efficacy of I plus HU was analysed in a Phase II study in GBM pts before progression was confirmed. As the role of enzyme-inducing anticonvulsive drugs in this setting is not clear only non-enzyme-inducing anticonvulsive drugs were allowed in this study.
Methods: From 2003, December up to 2005, June 30 non-progressive GBM pts were included, all of them in a phase of stable disease for more than 6 weeks following effective primary or secondary treatment after the first relapse including surgery, radiotherapie and at least one chemotherapeutic regimen. No enzyme-inducing anticonvulsive drugs were allowed. 600 mg of I and 1000 mg of HU were given as a continuous daily dosage, all pts were followed up by blood cell count weekly and magnetic resonance imaging every 6 weeks.
Results: In 2005, October all pts will be eligible for toxicity and 27 pts for 6 months progression free survival, 25 pts are male, 5 pts female, the median age is 44 years (32 to 71). All 30 pts had prior radiotherapy, 21 pts had temozolomide containing chemotherapy and 9 pts not temozolomide containing regimens only. The median observation time now is 10 months. 6 months PFS is 14 out of 18 pts so fare. Hematotoxicity grade 3 and 4 occurred in 13 out of 27 pts (leucocytopenia grade 3: 9 pts; leucocytopenia grade 4: 2 pts; thrombocytopenia grade 3: 6 pts) and required dose reduction of HU in 12 cases, dosereduction of I in 2 cases and G-CSF subcutaniously in 5 cases. There was no febrile neutropenia, no interruption of the study due to toxicity and no treatment related death.
Conclusion: In the examined regimen the combination of I (600 mg/day) and HU (1000 mg/day) was feasible but showed a significant higher rate of hematotoxicity compared to the combination with I 400 mg daily. The 6 months PFS data are promising, observation time, however, is short. Efficacy and toxicity data of the entire group of pts will be updated for the ECCO 2005 meeting.

503 POSTER

Cyberknife radiosurgery for spinal metastases

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Purpose/Objective: To determine the effectiveness and safety of Cyberknife radiosurgery in the treatment of spinal metastases.
Materials/Methods: From 1996 to 2003, 31 patients with 33 spinal metastases were treated using Cyberknife image-guided radiosurgery (Accuray, Inc., Sunnyvale, CA) at Stanford on an institutional review board-approved protocol. The goal of treatment was to deliver 16–25 Gy in 1–3 fractions, doses estimated to be effective based on prior experience in treating brain metastases of similar histologies. Patients were followed clinically and radiographically for at least 3 months or until death.
Results: After a mean follow-up of 10 months (range 0–22 months), 19 patients were alive and 12 were dead at last follow-up. No death was treatment-related. Fifty-four percent (14/26) of symptomatic patients experienced improvement of symptoms after treatment. Three patients developed clinical and radiographic signs of treatment-related spinal cord injury following treatment.
Conclusions: Cyberknife radiosurgery is effective and generally safe in the management of spinal metastases. The tolerance of the spinal cord to hypofractionated radiation within the range of doses administered in this study is not yet well understood. Prior chemotherapy or radiation may be additional confounding factors. At present, the ease of radiosurgical treatment and the effectiveness in alleviating pain must be weighed against the potential for spinal cord injury, especially for lesions of the thoracic spine.

504 POSTER

Tumor volume reduction from 3 Gy-fractions measured in brain metastases and implications for clinical trials of response modifiers

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Purpose: To calculate the dose necessary to control brain metastases with fractionated external beam radiotherapy (RT). Such data can guide the choice of doses in prospective clinical trials of RT alone or RT plus sensitising agents.
Methods: We determined the volume of 238 brain metastases in 81 patients treated with 10x3 Gy of whole-brain RT (WBRT) from serial pre- and post-treatment contrast-enhanced computed tomography (CT) scans. Imaging was performed within 14 days in 154 lesions, between 15 and 28 days in 72 lesions, and after > 28 days in all others. Furthermore, repeated CT scans after more than 1 month were available in 90 lesions.
Results: The median number of brain metastases per patient was 3 (range 1–5). Forty-two percent of the metastases showed solid contrast-enhancement, whereas 31% had ring-shaped contrast enhancement, i.e. central necrosis, of <50% and 27% had more central necrosis. The median pre-treatment volume was 2.6 ccm (range 0.03–85.5 ccm). A complete remission (CR) occurred in 24% of the lesions, whereas 3% showed further enlargement at first CT. The other lesions were either stable or smaller with a median volume reduction of 51%. Progression-free survival at 6 months was 100% in the CR group and 63% in the PR/NC group ($p < 0.05$). Regarding all 238 lesions, the median maximum volume reduction was 0.9 ccm. The best result was evident on scans obtained between 66 and 120 days after WBRT (median 1.5 ccm vs., for example, 0.6 ccm if the scans

were performed within 14 days, $p < 0.05$). Volume reduction was dependent of both initial volume and necrosis. Statistical modelling of these data after exclusion of lesions with short follow-up resulted in a group with a median initial volume of 5.3 ccm and a median maximum reduction of 3.1 ccm. Thus, each 3 Gy-fraction thus induces a volume reduction of 0.31 ccm. To make a lesion of 5.3 ccm (corresponds to a diameter of 2.15 cm) disappear on CT scans, an equivalent dose of 56 Gy in 2 Gy-fractions is needed.
Conclusions: Because permanent local control requires sterilisation of all clonogen tumor cells incl. those no longer visible on CT after macroscopic CR, even small lesions of just over 2 cm diameter should receive more than 28 fractions of 2 Gy. If 10×3 Gy is to be given together with a sensitising agent and the aim of inducing a CR, the agent must induce killing of the remaining $0.53-0.31 = 0.22$ cm of cells, which means increasing the effect of WBRT alone by 71%.

505 POSTER

Treatment of newly diagnosed high-grade glioma with concomitant and adjuvant temozolomide and radiotherapy – UK experience

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Background: In the UK the current management of high-grade gliomas is maximal surgical debulking followed by radiotherapy. It has been shown that the addition of temozolomide (TMZ) to radiotherapy significantly increases median survival (14.6 vs 12.1 months (Stupp et al, 2005 N Engl J Med 352 (10): 1036–8). Our centre has considerable experience with TMZ and has treated patients with a similar regimen. This study aims to confirm whether these results are replicated in practice in the UK.
Material and methods: We retrospectively reviewed 102 patients treated for high-grade gliomas with radiotherapy ± TMZ between 1998 and 2003. A search of our radiotherapy database and patient records was undertaken. Patients who were diagnosed with high-grade glioma and who did not receive radiotherapy or who only received a palliative dose were excluded from the study. Radiotherapy was administered to a dose of 60–65 Gy in 30–37 fractions over 6 weeks. TMZ was administered orally at a dose of 75 mg/m^2 daily for 6 weeks durig radiotherapy, followed by adjuvant TMZ for 6 cycles on days 1–5 of a 28-day cycle (150–200 mg/m^2/day).
Results: 102 patients (71 male, 31 female) with high grade gliomas were planned for treatment with radical radiotherapy (mean age = 52.6 years, range 21–72). 84 patients had glioblastoma multiforme (GBM), 18 had WHO grade III tumours. 53 patients underwent surgical debulking. 51 patients (50%) received concurrent TMZ and radiotherapy followed by adjuvant TMZ (median number of cycles = 3). 48 patients (47%) initially received radiotherapy alone but 10 of these received chemotherapy on disease progression. 3 patients died before treatment started. The choice of treatment options was partly historical (availability of TMZ) and partly the preference of the treating consultant. There were no identifiable patient factors influencing the decision for radiotherapy alone or combined treatment. Only 2 cases had grade III/IV haematological toxicity during concurrent treatment. Patients treated with concurrent TMZ and radiotherapy had a significantly better median survival by log-rank comparison of 12.5 months compared with 9 months for those treated with just radiotherapy ($p = 0.029$).
Conclusion: The addition of TMZ to the standard treatment of radiotherapy for high grade gliomas gives improved overall survival. This study shows that the published Phase III results can be replicated in everyday practice and that the regimen is both practical and effective.

506 POSTER

Shiga-like toxin inhibits cell viability and induce apoptosis in human glioma cells

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Tumour growth is due to an imbalance between cell proliferation and cell death. Increasing apoptosis (programmed cell death) is the most important mechanism for tumour cell death and tumour mass reduction during treatment with cytostatic drugs and irradiation. We therefore aimed at identifying mechanisms for induction of apoptosis by shiga-like toxin and to study its potential use for increasing the efficacy of tumour treatment. Shiga-like toxins have low adverse effects and are only cytotoxic to eukaryotic cells that express its cell surface receptor CD77. CD77 is over-expressed by several solid tumours such as breast carcinoma, ovarian carcinoma, and brain tumours.
We found that two glioma cell lines (U343 and SF767) that over-expressed CD77 also were sensitive for 0.001–5 ng/mL shiga-like toxin in a fluorometric cytotoxicity assay after 72 h incubation whereas other non-CD77-expressing cells were not. The cytotoxicity of the toxin was due to apoptosis as demonstrated by TUNEL staining after 48 h incubation using flow cytometry. 2 μmol/L of the CD77-receptor analogue PPMP (1-phenyl-2-hexadecanoyl-3-morpholino-1-propanol) eradicated CD77 expression after 3 and 6 days incubation and also completely inhibited shiga-like toxin cytotoxicity and apoptosis in both cell lines.
Our results suggest that shiga-like toxin may be used as a potent cytotoxic drug in the treatment of CD77-overexpressing tumours.

507 POSTER

A role of herpesviruses in brain tumor development?

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Background: Malignant gliomas are the most common primary brain tumors in humans and are generally rapidly fatal despite current therapies. Except for hereditary predisposition and high dose ionizing radiation, risk factors such as occupational, environmental or medical factors are controversially discussed. In addition, a role of viruses is suspected. Recently, Cobbs et al. (Cancer Res 2002, 62:3347–50) reported that of 27 gliomas tested, all expressed multiple gene products of HCMV in contrast to brain tissues from patients with meningioma, stroke, Alzheimer's and other brain diseases suggesting that HCMV might play an active role in glioma pathogenesis. Earlier sero-epidemiological case-control studies reported an inverse correlation of glioma cases with serum antibodies against varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and herpes simplex virus (HSV). HCMV antibodies were slightly more frequently observed in glioma cases than in population controls (Wrensch et al., Am J Epidemiol 2001, 154: 161–5). The present study was conducted to evaluate the role of previous herpesvirus infections in brain tumor development by (i) assessing the prevalence of HCMV gene products and/or nucleic acids in primary brain tumor tissues and corresponding blood samples, and also (ii) analyzing the sero-prevalence of anti-HCMV, anti-VZV, anti-EBV and anti-HSV IgM and IgG antibodies in patients with primary brain tumors.
Material and methods: Of 95 patients with primary brain tumors (gliomas, meningiomas, acoustic neurinomas, and medulloblastomas) biopsies from tumor tissues and blood samples were analyzed by a variety of nested PCRs for the presence of HCMV DNA, and sections of tumor tissues were analyzed by immunohistochemistry to detect HCMV-specific proteins. Furthermore, patients' sera were tested by ELISA for IgG and IgM antibodies to HCMV, VZV, EBV, and HSV, and compared to published prevalences.
Results: HCMV DNA was not detected, neither in the brain tumor tissues nor in the corresponding blood samples. Similarly, immunohistochemistry did not reveal any HCMV-specific proteins. Patients' sera were all were negative for IgM antibodies against the herpesviruses. IgG seroprevalences did not differ from published reference data in the German population.
Conclusion: The present study could not confirm the hypothesis that HCMV or other herpesviruses may play a role in glioma pathogenesis.

508 POSTER

Dexamethasone inhibit anti-cancer agent/radiation-induced apoptosis in C6 glioma cells

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Background: Dexamethasone, a synthetic glucocorticoid, is reported to induce partial resistance to anticancer drugs in glioma cells by transcriptional activation of Bcl-xL gene. In the present study, we investigated the upstream regulator of Bcl-xL gene which is activated by dexamethasone. And the effect of dexamethasone on radiation was also evaluated.
Methods and materials: For the induction of apoptosis in C6 glioma cells, 2 μM of camptothecin was added to the culture medium and up to 10 Gy of radiation irradiated onto cells. Western blot were performed to evaluate the effects of dexamethasone on Bcl-xL. Electrophoretic Mobility Shift Assay (EMSA) was conducted to assess DNA-binding activity of Stat5. To identify physical interaction between Stat5 and glucocorticoid receptor, Co-immunoprecipitation was performed. Cell viability was quantified by clonogenic assay and MTT assay. Apoptotic cell death was confirmed by a colorimetric caspase-3 assay with CaspACE™ (Promega), and DNA breakage by Cell death detection ELISA kit(Roche) or DAPI staining.
Results: Camptothecin alone increased caspase-3 activity up to 15.9 pmol pNA/μg/hour, in contrast to 3.5 pNA/μg/hour in untreated control cells. Increased caspase-3 activity by camptothecin was not seen in cells