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

G. Dresemann. *Franz-Hospital, Onkologische Abteilung, Dülmen, Germany*

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

G. Dresemann[1], C. Hosius[2], B. Weinkauf[2], Z. Nikolova[3], L. Letvak[4]. *[1]Franz-Hospital Dülmen, Onkologische Abteilung, Dülmen, Germany; [2]Novartis Pharma, Nürnberg, Germany; [3]Novartis Pharma, Basel, Switzerland; [4]Novartis Pharma, East Hanover, United States*

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

I.C. Gibbs[1], P. Kamnerdsupaphon[2], M. Ryu[3], R. Dodd[4], S. Chang[4], J.J. Adler[4]. *[1]Stanford University, Radiation Oncology, Stanford, CA, USA; [2]Chiang Mai University, Division of Therapeutic Radiology and Oncology, Faculty of Medicine, Chiang Mai, Thailand; [3]Kangnam St. Mary's, Department of Radiation Oncology, Seoul, Korea; [4]Stanford University, Neurosurgery, Stanford, CA, USA*

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

C. Nieder, N. Andratschke, A. Grosu, R. Thamm, M. Molls. *Klinikum rechts der Isar, Dept. of Radiation Oncology, Munich, Germany*

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