progenitor proliferation, and REST/NRSF, a transcriptional repressor of neuronal differentiation genes. Previous studies have shown that neither c-Myc nor REST/NRSF alone could cause tumor formation. To determine whether c-Myc and REST/NRSF act together to cause medulloblastomas, we used a previously established cell line derived from external granule layer stem cells transduced with activated c-myc (NSC-M). These immortalized NSCs were able to differentiate into neurons in vitro. In contrast, when the cells were engineered to express a doxycycline-regulated REST/NRSF transgene (NSC-M-R), they no longer underwent terminal neuronal differentiation in vitro. When injected into intracranial locations in mice, the NSC-M cells did not form tumors either in the cerebellum or in the cerebral cortex. In contrast, the NSC-M-R cells did produce tumors in the cerebellum, the site of human medulloblastoma formation, but not when injected into the cerebral cortex. Furthermore, the NSC-M-R tumors were blocked from terminal neuronal differentiation. In addition, countering REST/NRSF function blocked the tumorigenic potential of NSC-M-R cells.
Conclusion: Our findings indicate that abnormal expression of REST/NRSF and Myc in NSCs causes cerebellum-specific tumors by blocking neuronal differentiation and thus maintaining the "stemness" of these cells. Furthermore, these results suggest that such a mechanism plays a role in the formation of human medulloblastoma. Furhtermore, to our knowledge, this is the first study in which abnormal expression of a sequence-specific DNA-binding transcriptional repressor has been shown to contribute directly to brain tumor formation.

Poster presentations (Wed, 26 Sep, 09:00−12:00)
Central Nervous System

2506 POSTER

Investigation of histological correlate of ^{11}C-methionine (MET) PET uptake of brain gliomas by image fusion for navigated surgery

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Background: The objective of the study was to investigate the histological correlate of ^{11}C-methionine (MET) PET uptake of brain gliomas by image fusion for navigated surgery.
Methods: Twenty-seven patients (18 male, 9 female; mean age 42 years; range 11−77 years; 8 low-grade and 11 high-grade astrocytomas or mixed gliomas, 8 oligodendrogliomas) underwent MET PET studies preoperatively.
Results: MET PET tumor uptake was detected in 26 of 27 patients (96.3%). The quantitative MET tumor standardized uptake value (SUV) ratio was significantly higher in malignant gliomas and oligodendrogliomas than in low-grade gliomas (2.76 / 2.62 vs. 1.67, $p = 0.03$). Generally, qualitative visual grading of MET uptake revealed 2 main patterns: focal MET uptake in 12 and uniform global MET uptake in 11 patients. Focal uptake corresponded to malignant glioma histology in 66.7%, and uniform global uptake to oligodendroglial histology in 72.7%. In oligodendrogliomas, global MET uptake constituted 81.5% (range 53.8% and 135%) of the MRI T1 tumor volume on average and was limited to the MRI FLAIR tumor volume in 86% (7/8) of patients. Tissue samples of focal MET uptake areas correlated with histological anaplasia in 66.6% (8/12 glioma patients), although 62.5% (5/8 patients) lacked MRI contrast enhancement.
Conclusion: MET PET image fusion may facilitate targeting of anaplastic foci in homogeneous MRI-non-enhancing gliomas for biopsy, may identify oligodendroglial histology preoperatively as well as characterize biologically active tumor volumes within MRI T1/FLAIR tumor areas of patients candidates for resection.

2507 POSTER

Temozolomide (TMZ) concomitant to radiotherapy (RT) plus 12 cycles of maintenance chemotherapy in newly diagnosed GBM: is more better?

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Background: TMZ concomitant to radiotherapy followed by 6 cycles of maintenance chemotherapy improves median survival in newly diagnosed GBM. In the same group of patients, MGMT promoter methylation status has been correlated to improved survival and PFS. The aim of the present study was to assess the activity of TMZ concomitant to RT followed by 12 cycles of maintenance chemotherapy or up to a contrast enhanced MRS shows the presence of tumor. We also asses the correlation with MGMT promoter methylation status.
Materials: Adult patients with newly diagnosed histologically confirmed GBM were were treated with TMZ (75 mg/m^2/day) concomitant to radiotherapy (60 Gy/30F) followed by TMZ (150–200 mg/m^2 days 1−5, q28). We tested the relationship between MGMT promoter methylation status and clinical outcome of patients enrolled in the trial. MGMT promoter methylation was analyzed by methylation specific PCR (MSP).
Results: 104 consecutive patients (67 males), median age 53 (range 20−73), median KPS 90 were enrolled with a median follow up of 16 months (range 4−62). Of these 98.1% had a debulking surgery. Six patients (5.5%) discontinued chemotherapy for toxicity, and 64 (58.2%) for disease progression. The entire population obtained a median TTP of 11 months (95% CI: 8.5−13.5), and a median survival of 23 months (95% CI: 15.6−30.3). Median TTP and median survival were 29 months (CI 95% 20.0−38.0) and 38 months (95% CI: 20−56) respectively in methylated patients (32.7%) compared to 9 months (CI 95% 8.3−9.7) and 17 months (95% CI: 13−17) in unmethylated patients (67.3%) ($p < 0.0001$ both for TTP and MST).
Conclusions: A marked correlation between MGMT methylation status and clinical outcome has been showed in GBM patients treated with TMZ concomitant to RT followed by TMZ maintenance chemotherapy. The continuation of maintenance chemotherapy up to a lesion was present in MRS results in positive outcome in terms of survival. Further large studies would be required for more definitive conclusions on how long the maintenance chemotherapy should be delivered.

2508 POSTER

^{11}C-methionine-PET based substrate for target definition in stereotactic radiosurgery of brain metastases

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Purpose/Objective: Recently, target delineation in brain tumors, based traditionally on CT and MRI, has improved by using biologic imaging: ^{11}C-methionine positron emission tomography (MET-PET). However, no studies have so far quantified the tumor extension in MET-PET concerning the definition of targets in the stereotactic radiosurgery (SRS) of brain metastases. The purpose of this work is to investigate the recognition of a margin in the SRS of brain metastases by comparing these two imaging modalities using image fusion.
Materials and Methods: CT, gadolinium enhanced T1-weighted MRI and MET-PET were separately performed within 2 weeks in twenty patients with a total of 97 brain metastases for SRS treatment planning. The MET-PET and MRI studies were analyzed by two independent observers. These image sets (CT/MRI and CT/MET-PET) were then fused utilizing the Pinnacle System. The CT/MRI clinical target volume (CTV) (CTV-MRI) was defined as the contrast-enhanced area on CT/T1 gadolinium-MRI fusion images. CT/MET-PET CTV (CTV-MPET) was defined as the area of an accumulation of CT/MET-PET, which was apparently higher than that of normal tissue on CT/MET-PET fusion images. A threshold value for the tumor/normal tissue index of 1.7 was considered for the tumor in all lesions. In addition, CTV-MRI-1 mm, CTV-MRI-2 mm, CTV-MRI-3 mm and

CTV-MRI-5 mm were defined as CTV-MRI plus 1 mm, 2 mm, 3 mm and 5 mm margins, respectively.
Results: CTV-MRI < 0.5 cc: The sensitivity of tumor detection of MET-PET was 43% (18/42). In 18 lesions, the mean CTV-MRI and CTV-MPET were 0.23 cc and 0.54 cc, respectively. In 18 (100%) of the lesions, the CTV-MPET was located within the CTV-MRI-1 mm.
0.5 cc < CTV-MRI < 2.5 cc: The sensitivity of tumor detection of MET-PET was 95% (18/19). The mean CTV-MRI and CTV-MPET were 1.01 cc and 1.80 cc, respectively. In 17 (95%) lesions, the volume of CTV-MPET extended beyond the CTV-MRI-1 mm was less than 1 cc. In 18 (100%) lesions, CTV-MPET was located within CTV-MRI-2 mm.
2.5 cc < CTV-MRI < 5.0 cc: The sensitivity of tumor detection of MET-PET was 100% (18/18). The mean CTV-MRI and CTV-MPET were 3.36 cc and 4.84 cc, respectively. In 17 (95%) lesions, the volume of CTV-MPET extended beyond the CTV-MRI-2 mm was less than 1 cc.
5 cc < CTV-MRI: The sensitivity of tumor detection of MET-PET was 100% (17/17). The mean CTV-MRI and CTV-MPET were 15.24 cc and 18.41 cc, respectively.
In 14 (82%) lesions, the volume of CTV-MPET extended beyond the CTV-MRI-3 mm was less than 1 cc. In 100% of lesions, CTV-MPET was located within CTV-MRI-5 mm.
Conclusion: On defining the target volume definition in the SRS planning of brain metastases, this ^{11}C-methionine PET study indicates that a margin of 1 mm (CTV-MRI < 0.5 cc), 1−2 mm (0.5 cc < CTV-MRI < 5.0 cc) and 3 mm-5 mm (5 cc < CTV-MRI) should therefore be added to MRI studies.

2509 POSTER

Phase II study of fixed dose rate gemcitabine as radiosensitizer for newly diagnosed glioblastoma multiforme (GBM): preliminary results

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Background: Gemcitabine is a deoxycytidine analogue with a wide range of antitumour activity, presenting powerful radiosensitizing activity at non-cytotoxic concentrations. On this basis, several phase I/II studies have presently been designed on different tumours with concurrent radiation therapy. In malignant glioma few data are presently available on the effects of gemcitabine, with unsatisfactory results as a single antiblastic agent. In a previous phase I study, conducted in our Institution, where fixed dose rate (FDR) gemcitabine at 10/mg/m^2/min was tested in association with radiotherapy (RT) for the treatment of newly diagnosed GBM, a maximum tolerated dose of 175 mg/m^2/wk was identified. Observed activity has been considered interesting enough to support a phase II study.
Materials and Methods: After surgery for GBM, patients presenting measurable residual tumour were treated with fractionated focal RT at a daily dose of 2.0 Gy per fraction, five days per week for six weeks (total dose of 60 Gys). FDR gemcitabine at 175 mg/m^2/wk was given concomitantly starting 24−72 hours prior to RT, and then for the whole duration of RT. MRI evaluation was performed at 7 and 40 days from the end of chemo-radiotherapy for early therapeutic assessment. Standard oral temozolomide 150–200 mg/m^2 was administrated following the combined experimental treatment, at least until tumour progression or relevant side effects. Tumour response rate, progression free survival, and overall survival time have been considered as main objectives.
Results: From 07/2004 16 patients (9 male, 7 female) have been enrolled. Characteristics of patients were: median age 57 years (42−72), median KPS at baseline 90 (70–100), surgery/biopsy 14/2. Median time from diagnosis to the initiation of gemcitabine was 45 days (28−54). Among the 14 evaluable patients 3 (21.4%) partial responses, 7 (50%) stable disease and 4 (28.5%) progressive diseases were recorded. At a median follow up of 18 months (2−33) time to tumour progression was 6 months (1.5−24). Toxicity was manageable with only one G3 neutropenia and hypertransaminasemia in two patients respectively. Grade 1 hypertransaminasemia was registered in 6 patients (43%).
Conclusions: These preliminary results show that in patients with newly diagnosed GBM, radiosensitizing FDR gemcitabine at 175 mg/m^2/wk is a well tolerated regimen with an interesting activity. Accrual is ongoing and more extensive results will be presented.

2510 POSTER

Radiosensitized treatment of metastatical brain tumours with hematoporphyrin derivative

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Background: The aim of this work was to investigate and to enlarge the possibilities of sensitized malignant tumor treatment using some derivatives of hematoporphyrin (HpD) as a radiosensitizer. In this paper we have reviewed our results of radiosensitized treatment (RST) of metastatical brain tumors.
Materials and Methods: From 2000 to 2006 the total of 33 patients with metastatical brain tumors underwent RST. HpD was injected i.v.; 24, 48 and 72 h after injection of the sensitizer tumors were irradiated with gamma rays 2 Gy at a time from radioactive ^{60}Co (the full dose of the course was 6 Gy). 7 patients underwent a single course of RST, for the rest RST was repeated.
Results: The primary result was already noticeable during the treatment. Especially rapid effect was observed in the patients, who had been in a critical condition. 9 of these 14 patients began to walk, to speak and even to read within two weeks. Nausea disappeared in 8 patients. The Karnofsky performance scale index increased immediately after RST in 29 patients. As the immediate result of RST of metastatical brain tumors all malignant brain tumors (22) in 8 patients fully disappeared. In 6 patients 13 tumors disappeared after a single RST course, and in 2 patients 4 tumors disappeared after some RST courses. However the recurrent disease – new brain metastasis was noticed in three patients. The repeated single RST course was sufficient for the complete regression of all brain metastases in two patients. CT or MRI examinations, provided 3−6 weeks after each RST course, revealed the regression of tumor in 27 patients. As the result of RST, 9 patients were without metastatical brain tumors for 74, 51, 14.5, 12.5, 12, 10, 9, 6 and 5.5 mo. after RST. The median survival of patients (from the moment of brain metastases detection) treated by the addition of RST was 15 mo. Comparing it with the 4.5 mo. median survival of 171 control group patients, it was statistically significant longer. The median survival of patients from the first course of RST was 9 mo.
Conclusions: RST is a new and effective method of treatment in metastatical brain tumors. The effectiveness of RST depends on the morphological type of tumor.

2511 POSTER

Imatinib plus hydroxyurea in pretreated non-progressive glioblastoma (GBM) – a single center phase II study

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Background: GBM is a highly malignant brain tumor with a median survival of about 15 months. Dysregulated signalling of platelet derived growth factor receptors (PDGF-Rs) is implicated in pathogenesis. The combination therapy of Imatinib (I) plus Hydroxyurea (HU) showed impressive efficacy and tolerability in patients (pts) with recurrent progressing GBM. In a pilot group of 30 pts with recurrent GBM the progression free survival at 6 and 24 months was 32% and 16% respectively. Disease stabilisation (SD) was achieved in 37%. Prolonged disease stabilisation for more than 2 years was possible. Despite the aggressive course of GBM, short periods of disease stabilisation after primary treatment or effective treatment of relapse are observed. The current Phase II study was conducted to analyze the efficacy of I plus HU treatment in GBM pts with documented disease stabilisation for at least 6 weeks as maintenance treatment.
Methods: From December 2003 up to June 2005 30 non-progressive GBM pts were included, all of them with SD for more than 6 weeks following effective treatment, including surgery, radiotherapy and at least one chemotherapeutic regimen. No enzyme-inducing anticonvulsive drugs were allowed. I at the dose of 600 mg od and 1000 mg of HU (500 mg bid) were given as a continuous daily treatment, all pts were followed up by blood cell count weekly and magnetic resonance imaging every 6 weeks.
Results: All 30 pts are eligible for safety and for 6, 12 and 24 months progression free survival (PFS) and overall survival (OS); 25 pts are male, 5 pts female, the median age is 44 years (32 to 71), 24 pts had primary and 6 pts secondary GBM. All 30 pts had prior radiotherapy, 21 pts had temozolomide containing chemotherapy and 9 pts non-temozolomide containing regimens only. 8 pts were free from relapse, 17 pts after first and 5 pts after second relapse. The median observation time is 31 months. 6, 12 and 24 months PFS is 60% (18/30), 40% (12/30) and 17% (5/30) respectively. 6, 12 and 24 months OS is 90% (27/30), 67% (20/30) and 37% (11/30) so far. PFS for more than 24 months occurred in 3/6 pts with secondary and in 2/24 pts with primary GBM. Hematotoxicity grade 2