2502 ORAL

Does initial response to corticosteroids predict survival in primary CNS lymphoma (PCNSL)?

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Background: Corticosteroids alleviate symptoms from vasogenic edema in patients with PCNSL and have direct cytotoxic effects on tumor cells. It is not clear whether an initial response to corticosteroids predict patient outcome after definitive treatment.
Materials and Methods: Among 338 PCNSL patients treated in our institution since 1986, descriptive variables and impact of initial response to corticosteroids on OS and FFS were studied in 98 patients.
Results: The median age was 63 years and median KPS was 70. Men constituted 47% of the patients. Median follow-up for survivors was 30 months. Histologically, 69% had a diffuse large B cell lymphoma. Brain, CSF and ocular involvement were present in 100%, 22% and 15% of patients, respectively. We observed an objective radiographic response (CR plus PR) in 53% of patients after initial corticosteroids. Most patients were treated with MTX based regimens (85%), radiation therapy (61%) and high dose cytarabine (51%), independent of the initial response to corticosteroids. Five-year OS was 35% and five-year FFS was 26% for all 98 patients. There was no significant difference in OS and FFS between radiographic responders and non-responders after initial corticosteroids. There was also no significant difference in median age, initial KPS, time to definitive treatment between two groups.
Conclusion: A significant number of PCNSL patients had an initial response to corticosteroids. However, this response is not a good prognostic factor.

2503 ORAL

Erlotinib (E) versus temozolomide (TMZ) or BCNU in recurrent glioblastoma multiforme (GBM): results from a randomized phase II trial (EORTC 26034)

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Background: Epidermal growth factor receptor (EGFR) is amplified in 40–50% of GBM cases and is often constitutively activated (EGFRvIII mutant), making it a potential therapeutic target. EGFR tyrosine-kinase inhibitors have shown promising activity in recurrent GBM, particularly in specific molecular subsets. We report results from a randomised phase II study of erlotinib (Tarceva®) in recurrent GBM.
Methods: Eligible patients (pts) had histologically proven GBM, recurrent >3 months after radiotherapy, Karnofsky performance status (KPS) $\geqslant$70, no prior chemotherapy for recurrent disease and an available tissue sample for EGFR analysis. Treatment was E 150 mg/day (300 mg/day if on enzyme-inducing anti-epileptic drugs [EIAEDs]), or control (TMZ 150–200 mg/m^2, day 1–5 q4wk or BCNU 60–80 mg/m^2 i.v., day 1–3 q8wk). E dose escalation to 200 mg (500 mg in pts on EIAEDs) was done in the absence of significant toxicity. Response was assessed using Macdonald's criteria, the primary endpoint was 6 months' PFS; P0 was set at 15% and P1 at 30%, sample size was 2 x 50 pts. EGFR amplification and expression of EGFR, EGFRvIII and PTEN were assessed by FISH and IHC, respectively. Adverse events (AEs) were monitored.
Results: 110 pts were randomised (54 E; 56 control: 27 TMZ; 29 BCNU), with a median age of 55 years and median KPS of 90. 109 pts commenced treatment, with E pts receiving a median 2 cycles of treatment, TMZ pts receiving 4 cycles and BCNU pts receiving 1 cycle. Few E-related grade 3/4 AEs were reported: 5 dermatological AEs and 1 haemorrhage, with only 3 pts discontinuing E due to toxicity. Grade 3/4 haematological toxicities were the most frequently reported AEs for control pts (3 with TMZ, 13 with BCNU). In the control group, 2 responses were observed, while the best response seen with E was SD in 6 pts. Six-month PFS was 12% for E and 24% for control. Similar 6- and 12-month OS were seen across both treatment arms (61% and 24% for E and 63% and 26% for control). Pts with EGFRvIII mutations (13 for E arm, 8 for control) had shorter PFS ($p = 0.007$) and OS ($p = 0.004$), irrespective of the treatment received. Neither EGFR expression, EGFR amplification nor EGFRvIII mutation status were correlated with response or PFS on E therapy.
Conclusion: The results of this randomised, controlled phase II study did not demonstrate sufficient activity for erlotinib in the general recurrent GBM population. EGFRvIII mutation status was not predictive of response to erlotinib.

2504 ORAL

Networking of endogenous modulators of nuclear factor-kappaB in predicting outcome in high-grade gliomas

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Background: Nuclear factor-kappaB (NF-κB) is a eukaryotic transcription regulator at the crossroad of a cell's decision to live or die. Excessive and prolonged activation of NF-κB has been established as a principal mechanism of tumor chemoresistance, which is primarily mediated by its antiapoptotic activity. The activity of NF-κB is regulated by a complex network of endogenous pathway modulators, which under normal cell conditions keep NF-κB in an inactivated state. We have discovered alterations in several NF-κB pathway modulators in glioblastoma cells, which may act synergistically in activating NF-κB during resistance formation to temozolomide, including the TNFAIP3, NFKBIA, and TNIP1 genes.
Materials and Methods: We have evaluated the outcome relationship for these and additional endogenous modulators of canonical NF-κB activation in four independent high-grade glioma cohorts comprising more than 200 tumors.
Results: We here confirmed the putative importance of NF-κB pathway activation status in predicting high-grade glioma outcome. Our data indicate an increasing complexity and linkage of several modulatory molecules (TNFAIP3, NFKBIA, TNIP1, and TNIP2) to patient outcome that interact physical and functionally in a cooperative fashion to regulate NF-κB activation. We found that for many of these molecules combined predictor models outperform the predictive power of the individual molecules. This observation is consistent with recent evidence suggesting the cooperation of these endogenous inhibitors in a negative feedback regulation of NF-κB activation and a mutual facilitation of their repressive ability. In terms of outcome prediction, we found several of these inhibitors to outperform established clinical and morphological prognostic variables such as patient age and tumor grade (III vs. IV), as well as the O6-methylguanine DNA methyltransferase (MGMT) gene, the currently most established outcome marker in glioblastomas. We further found that treatment failure with temozolomide in initially sensitive tumors is associated with significant changes in the abundance of these endogenous modulators in such a way that we would predict the tumor to be resistant to the drug.
Conclusions: These findings raise the hope for this endogenous regulatory network as an amenable target to modulate NF-κB-mediated resistance in high-grade glioma cells, with the ultimate goal of increasing the efficacy of temozolomide in patients harboring these challenging tumors.

2505 ORAL

Abnormal expression of REST/NRSF and Myc in neural stem/progenitor cells causes cerebellar tumors by blocking neuronal differentiation

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Background: Medulloblastoma, one of the most malignant brain tumors in children, is thought to arise from undifferentiated neural stem/progenitor cells (NSCs) present in the external granule layer of the cerebellum; However, the mechanism of tumorigenesis remains unknown for the majority of medulloblastomas.
Materials and Methods: We used human medulloblastoma patient samples, mouse cerebellar stem/progenitor cells (NSCs) and mouse models to attain our objective.
Results: We found that many human medulloblastomas express significantly elevated levels of both myc oncogenes, regulators of neural

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