Conclusion: We have discovered novel drugs that can significantly inhibit the viability and growth of human glioma stem cells. These findings are expected to either replace or complement existing therapies within a clinical setting in due course.

8755 POSTER

NPAS3 is a Negative Prognostic Survival Marker in Glioblastomas

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Background: Glioblastomas, the most common primary brain tumours in adults, still continue to have a predominantly fatal outcome. We previously cloned NPAS3 (Neuronal PAS 3), a gene which is among the largest genes in the human genome, and encodes a transcription factor. We recently discovered NPAS3 drives the progression of malignant astrocytomas, as a tumour suppressor, by modulating the cell cycle, proliferation, apoptosis, cell migration/invasion, and with a further influence on angiogenesis. In human glioblastoma surgical specimens, up to 75% demonstrate aberrant NPAS3 protein expression. In this study, we evaluated the expression of NPAS3 in the overall survival of patients diagnosed with glioblastomas.
Methods and Results: We examined a panel of glioblastomas from 77 post-operative patients who had total resection of the tumour. Post-operative patients were treated by standard adjuvant radiation therapy (60 Gy, 6 to 7 weeks) combined with chemotherapy, with a study follow up not exceeding 30 months. Among the glioblastomas, 28 had absent, 18 had elevated and 31 had normal NPAS3 expression. 54 males and 23 females were used in this study with a median age of 59 years. From this study, patients with glioblastomas having absent NPAS3 expression were identified with the poorest overall survival in comparison to patients with glioblastomas having normal or elevated NPAS3 expression (Log-rank P-value <0.001). Such trend is still maintained even when patients are stratified among different age groups (<60, >60 years). However, no significant difference in overall survival among patients with glioblastomas having either normal or elevated NPAS3 expression was noted (Log-rank P-value >0.05). Likewise, no significant difference in gender verses overall survival noted.
Conclusion: Our findings are of clinical importance by demonstrating that NPAS3 is an informative negative prognostic survival marker in patients with glioblastomas.

8756 POSTER

Correlation of Epidermal Growth Factor Receptor and Phosphatase and Tensin Homolog Status With Treatment Outcome in Postoperative Glioblastoma Patients Treated With Chemoradiotherapy

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Background: To study the impact of Epidermal Growth Factor Receptor (EGFR) overexpression and loss of phosphatase and tensin homolog (PTEN) expression on treatment outcome in Glioblastoma (GBM) patients.
Materials and Methods: Twenty patients of GBM treated with maximal safe resection followed by concurrent chemoradiotherapy were analyzed in this prospective single arm study. All patients underwent a maximal safe resection. Clinical Target Volume (CTV) for radiotherapy included the pre-operative tumour volume and surrounding edema with 2.5 cm margin. A uniform 5 mm expansion was used to generate Planning target volume (PTV). A dose of 60 Gy to the PTV was prescribed at 95% isodose level with 6MV photons using conformal radiotherapy. All patients received concurrent Temozolomide at 75 mg/m^2 daily during the whole course of radiotherapy and six courses of adjuvant chemotherapy with Temozolamide 175–200 mg/m^2 D1−5 given every 4 weeks. EGFR and PTEN assessment was done by Immunohistochemistry(IHC). Proteinase-K (DAKO) and antigen retrieval buffer citrate(Neo-marker) were used for EGFR and PTEN respectively. Response evaluation was done one month after completing treatment using RECIST criteria for solid tumours version 1.1.
Results: Twenty biopsy proven GBM patients included in the study (male: Female-3:1). Median age 45 years (range: 18−57 years). Commonest presentation was headache (11) followed by seizure (9). Frontal lobe (9) was the commonest site followed by temporal lobe(7). The median KPS was 90 (Range-70–100). Thirteen patients underwent a complete resection and partial resection was possible in seven. Sixteen blocks were retrieved with adequate specimen for IHC. In this cohort four (25%) cases were found to over express EGFR protein whereas loss of PTEN expression was noted in one (6.25%) case only. 95% of our patients completed the planned treatment one patient defaulted after two cycles. One patient developed grade IV thrombocytopenia and another patient developed grade III thrombocytopenia. The overall grade III and grade IV thrombocytopenia was noted in 10% of patients. In our study complete response was noted in 45% patients whereas 15% had a partial response only. After a median follow-up of 15.7 months the median survival found to be 17.7 months (range-6 months-27 months) and disease free survival was 21.9 months. We found a trend towards overall survival benefit for patients who underwent a complete resection but due to small sample size the p value was not significant. OS and DFS were found to differ significantly with KPS, age, EGFR overexpression and loss of PTEN.
Conclusion: Only a small subgroup of Indian patients with GBM may show EGFR over expression and loss of PTEN. Combining targeted therapy to radiotherapy may help improve treatment results in this subgroup. A larger prospectively designed study is needed to answer this question.

8757 POSTER

Intrathecal Sodium Butyrate for Neoplastic Meningitis- Experimental Study and Clinical Trial

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Background and Purpose: The prognosis of neoplastic meningitis (NM) is still extremely poor, and thus a new treatment method has been anticipated. Sodium butyrate (SB)-C-4 saturated fatty acid present in the human bowel membrane in high concentration (2mM) as food metabolite, has been reported as biological inducer of differentiation of several cancer cells resulting in growth arrest. However, the precise mechanism has not been fully elucidated. Here, we firstly investigated the role of this natural chemical on cancer cell motility and invasion. Secondly, continuous intrathecal administration of SB for rat NM was evaluated, and finally we performed clinical study under thepermission of local ethics committee.
Experimental Design and Results: In vitro, we examined the cytotoxicity, colony formation in soft agar, neurotoxicity using a primary culture of ED14 neurons and cultured astrocytes. We also investigated the inhibitory effect of this compound on tumour cell invasion with the Matrigel invasion assay. As a result, SB inhibited rat breast cancer (Walker 256) and human glioblastoma (A172) cell motility and invasiveness, decreased 2D cell growth and colony formation in soft agar in a dose-dependent fashion, and showed minimal neurotoxicity as well as same grade of influence on cultured astrocytes. SB also affected the morphology of cells namely spread out, decreased peripheral ruffling and increased stress fiber formation. The phosphorylation level of focal adhesion kinase (FAK, pY577 and pY397 sites) was increased, but that of myosin light chain was not affected. All of these biological effects of SB were reversible, and recovered after withdrawal. In addition, A172 cells treated with SB showed positivity for senescence-associated b-gal staining with elevated expression level of p53 and p21 proteins in a dose-dependent manner. In vivo, neurotoxicity was evaluated by continuous intrathecal administration of SB using osmotic pump in syngeneic normal rat, and no abnormal findings were observed. Moreover, invasion of cells into brain parenchyma was inhibited and the extended animal survival was observed in experimental rat NM model using Walker 256 cells. Finally, clinical study was performed in patients with NM, and continuous intrathecal administration showed good treatment effect without severe adverse effects.
Conclusion: SB induced cellular senescence, inhibited invasion and growth, and would be a good candidate for NM without severe adverse effects.

8758 POSTER

B-Aware − a Unique Patient Awareness Campaign to Improve Outcomes in Patients With Metastatic Brain Tumours

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Background: More than 1 million Americans are diagnosed with cancer every year and up to 200,000 of these patients develop metastatic brain tumours (MBTs) during the course of their illness. Early diagnosis of MBTs and improving the patient's awareness of potential treatment options is likely improve the outcomes of these patients. We report on a direct-to-cancer patient education program on the risks, symptoms and treatment options regarding MBTs.
Method: The campaign, called B-Aware^{SM} (B is for brain), is the first program of its kind, launched by Cleveland Clinic in partnership with the Northern Ohio American Cancer Society. The program strives to educate cancer patients and their families about the risk as well as common signs and symptoms of MBTs with the goal that this awareness may

lead to early detection of MBTs. It also informs the patient and their families about multiple modality therapy options for patients with BM including surgery, radiation, radiosurgery and chemotherapy so that they may get more tailored treatment. B-Aware[SM] patient brochures have been circulated throughout Cleveland Clinic cancer centers to help improve patient education. A dedicated webpage (www.clevelandclinic.org/b-aware) has been created to further this endeavor and information may be obtained through the American Cancer Society. There is also a dedicated patient hotline that answers the questions that patient or their families may have regarding MBTs.
Conclusion: B-Aware[SM] is a unique program that has stemmed from a partnership between a tertiary care center (Cleveland Clinic) and the American Cancer Society that endeavors to improve the outcomes of patients with MBTs by improving the awareness of potential patients regarding the risks, signs and symptoms of MBTs and the therapy options for such patients.

8759 POSTER

A Brain Cancer Pathway − 2 Years Experience in Clinical Practice

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Background: The Danish Health Care Sector seeks to improve cancer survival through better diagnostics, faster treatment and increased focus on cancer prevention and early help-seeking. In neuro-oncology this has resulted in the National Integrated Brain Cancer Pathway (NIBCP). We analyze how the pathway works in the initial phase in a clinical setting with emphasis on referral manner and pathway criteria.
Materials and Method: All patients admitted during the first 2-year period to a regional neurology department in Denmark and fulfilling the NIBCP inclusion criteria were included. The clinical inclusion criteria encompass recent onset of focal neurological symptoms or epileptic seizures, changes in personality or behavior or cognitive deterioration or marked changed in headache pattern and in all cases symptoms progressing over time without any other likely cause.
Data regarding referral, symptoms, diagnosis and time for work-up was obtained and supplemented by retrospective review of patient charts. Sensitivities, specificities and positive predictive values of the inclusion criteria were calculated with MRI scan of the cerebrum as index of validity.
Results: The strength of the pathway inclusion criteria is found to be determined largely by the number of criteria fulfilled and by which symptoms predominate at the time of admission. The criteria are found to pick up on the majority of patients with symptomatic brain malignancy but are also found to be highly sensitive of general structural brain lesions.
Conclusion: The pathway is a major step forward in the effort of optimizing the illness trajectory for brain cancer patients. More patients suspected of brain cancer are expected to go through expedient work-up as general practitioners become increasingly familiar with the pathway.

8760 POSTER

Should the Management of Brain Metastases Be Influenced by the Age of the Patient?

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Objectives: The radiation Therapy Oncology Group (RTOG) defined age as one of the key factors predicting survival time in patients with brain metastases treated with whole brain radiation therapy (WBRT). As most patients with BM succumb from the intracerebral manifestation of their disease we hypothesized that the likelihood of distant recurrences should be higher in elderly patients.
Method: All visible brain metastases were treated with Gamma Knife® surgery (GKS) in 1397 patients treated in St. Elisabeth Hospital, Tilburg, The Netherlands and West Virginia University, Morgantown, WV, USA, All patients were followed prospectively with MR imaging every 3rd months as long as deemed clinically meaningful. The time at risk for distant recurrences was defined as the time between GKS and the first of the following event: the diagnosis of a distant recurrence, the time to death, the time to the last information of the patient or treatment with WBRT without evidence of distant recurrences.
Results: There was no significant relation between the risk of developing distant recurrences and age ($P = 0.033$) comparing $<$ to $\geqslant$ 65 years of age. However, the difference became significant when 75 years was used as age limit ($P = 0.0074$).
Conclusions: Age has a predictive value not only for predicting survival but also for intracranial tumour control following GKS. However, a relavant age limit should probably be older than the 65 years set by RTOG.

Oral Presentations (Sat, 24 Sep, 11:15−13:35)
Lung Cancer − Metastatic

9000 ORAL

Epidermal Growth Factor Receptor (EGFR) Expression as a Predictive Biomarker of Survival in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Receiving First-Line Therapy With Cetuximab Combined With Chemotherapy in the FLEX Trial

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Background: The phase III FLEX study showed that the addition of cetuximab to first-line chemotherapy (CT) statistically significantly improved overall survival (OS) in patients with EGFR-expressing, advanced NSCLC. Prospectively collected tumour immunohistochemistry (IHC) data were analyzed to investigate whether EGFR expression was predictive of outcome in FLEX study patients.
Material and Methods: Tumour EGFR expression was assessed in 1121 (99.6%) of 1125 FLEX study patients according to the proportion of positive cells and intensity of membrane staining on a continuous IHC scale of 0–300. A discriminating threshold IHC score of 200 was selected and used to define groups with low (IHC score <200) and high (IHC score $\geqslant$200) EGFR expression, as previously described. The OS benefit in each group was further analyzed for the overall population and for subgroups defined by tumour histology.
Results: High tumour EGFR expression was scored for 345 (30.8%) of 1121 patients. Baseline characteristics were comparable between treatment arms in both high and low EGFR expression groups. OS time was prolonged in the high EGFR expression group in the CT plus cetuximab compared with CT arm (median 12.0 vs 9.6 months; hazard ratio, HR, 0.73; $p = 0.011$). No corresponding OS benefit was observed in the low EGFR expression group (median 9.8 vs 10.3 months; HR 0.99; $p = 0.88$). A treatment interaction test assessing the difference in HRs between the EGFR expression groups yielded a p-value of 0.044. A multivariable analysis of OS in the EGFR expression groups with adjustment for prognostically relevant baseline factors confirmed the results of the unadjusted analysis. The OS benefit in the high EGFR expression group was observed across tumour histologies: squamous cell carcinoma (median 11.2 vs 8.9 months; HR 0.62); adenocarcinoma (median 20.2 vs 13.6 months; HR 0.74); other histologies (median 8.0 vs 7.6 months; HR 0.75). The safety profile for CT plus cetuximab in the high EGFR expression group was similar to that seen in the overall safety population, with no unexpected adverse events.
Conclusions: The addition of cetuximab to first-line CT substantially prolonged OS in patients with advanced NSCLC and high tumour EGFR expression regardless of histological subtype. The selection of those patients most likely to benefit from first-line treatment with CT plus cetuximab should be based primarily on whether tumours express high or low levels of EGFR, as defined in the current analysis.

9001 ORAL

A Retrospective Subgroup Analysis of EGFR Immunohistochemistry (IHC) Expression by Histo-Score Correlated to Outcomes From the BMS099 1st Line Phase III NSCLC Trial of Cetuximab (Cet) Plus Carboplatin/Taxane

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Background: The phase III FLEX study showed that the addition of Cet to first-line chemotherapy (CT) significantly improved overall survival (OS) in patients (pts) with EGFR-expressing, advanced NSCLC. The phase III BMS099 trial investigated Cet plus first-line CT in advanced NSCLC pts regardless of EGFR expression. In BMS099, the primary end point, progression-free survival (PFS), did not differ significantly between