8751 POSTER

Phase II Study of Bevacizumab in Combination With Temozolomide as Treatment of Patients With Recurrent Glioblastoma Multiforme: Preliminary Analysis of Toxicity

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Background: In recurrent glioblastoma (GBM), the combination of bevacizumab with irinotecan reported a significant improvement of response rate and 6-month progression free survival (PFS 6). However, there are limited data on safety and efficacy of bevacizumab in combination with other widely used chemotherapy agents such as temozolomide. The aim of this study is to evaluate the efficacy of the combination of bevacizumab and temozolomide on a week on/week off schedule.
Methods: We report here the toxicity profile of the first 10 patients treated in a Spanish phase II multicenter, open-label study in pts with recurrent GBM who were treated with temozolomide 150 mg/m^2 d1−7 and 15−21 and bevacizumab 10 mg/kg d 1 and 15 q28 for 6 cycles (and bevacizumab maintenance thereafter), until tumour progression or unacceptable toxicity. Primary endpoints of the study are PFS 6 and toxicity (evaluated according to NCI CTC v3.0 criteria).
Results: From June 2010 to January 2011, 17 evaluable pts were recruited in 8 sites. This safety analysis was realized when the 10 first patients have received at least two cycles of treatment. Patient characteristics: median age was 57.5 (43−64), male/female: 4/6, ECOG 0−1 90%, totally/partially resected 4/6. All pts progressed after Stupp's regimen. At the study entry, seven patients were on dexamethasone at inclusion: median 6 mg (2−8 mg). Only 2 patients presented toxicities grade 3−4: enteritis (1, g3), intracranial hemorrhage (1, g4), upper respiratory infection (1, g3), urinary tract infection (1, g3), thrombosis (1, g3) and olfactory nerve disorder (1, g3). One patient had to stop the treatment due to an adverse event (intracranial hemorrhage).
Conclusions: Treatment with bevacizumab and a week on/week off temozolomide schedule shows an acceptable toxicity profile treatment in recurrent glioblastoma. The trial is ongoing.

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Bevacizumab After First Line Treatment in Malignant Glioma

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Background: Treatment options of recurrent malignant glioma (MG) are very limited and with a poor survival benefit. MGs are highly vascular tumours and represents potentially promising target for anti-vascular endothelial growth factor therapies. Results from phase II trials suggest that the combination of bevacizumab and irinotecan is beneficial to patients (pts).
Material and Methods: Thirteen pts with recurrent MG were treated with bevacizumab in combination with irinotecan. All patients received bevacizumab at 10 mg/kg in combination with irinotecan 340 mg/m^2 or 125 mg/m^2 (with or without concomitant enzyme inducing antiepileptic drugs, respectively) every two weeks. Patient clinical characteristics, drug toxicities, response, PFS and OS were evaluated.
Results: Pts characteristics bar were: 9 men and 4 women, median age of 38 years (range 22−55). 7 pts had glioblastoma multiforme, 5 anaplastic astrocitoma and 1 anaplastic oligoastrocytoma. As an initial therapy 11 people had a standard therapy with primary resection followed by adjuvant chemoradiotherapy. One pt had no surgery, one had no concomitant chemotherapy (Cht). The mean number of prior Cht was 1.38 (range 1−3). Average WHO performance status was 1.23 (range 0−2). In our group average number of Cht applications were 9.8 (range 1−17). Radiological response after 3 months was observed in 9 (69%) patients (1 complete response, 8 partial response). 2 pts had stable disease, 2 pts have progressed. The median time to disease progression was 5.9 months, 6-months PFS rate 53.8%. The median OS was 7.1 months. 6-months OS rate was 69.2%. 11(85%) pts had grade 1 toxicity (neutropenia (1pt), lymphopenia (5pts), thrombocytopenia (1pt), anemia (2pts), hypertension (2 pts), proteinuria (2pts), vomiting (1pt), and diarrhea (1pt)) but there was only one case of grade 2 and 3 toxicity (proteinuria). There were no grade 4 toxicity, no trombembolic event and no intracranial hemorrhage observed.
Conclusion: In patient with recurrent MG bevacizumab in combination with irinotecan is an active regimen with acceptable toxicity. PFS, OS and 6-months survival rates observed in our group are similar to other previous reported bevacizumab-irinotecan trials in MG and indicate a trend to better survival.

8753 POSTER

Experience With CPT-11-Bevacizumab in Patients With Recurrent Malignant Glioma in Puerta del Mar Hospital

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Background: Currently there is not a standard therapy for recurrent high grade gliomas, however, Bevacizumab has shown promising activity in recurrent malignant glioma.
Recently, phase II studies with bevacizumab have shown efficacy assessed in terms of radiological response rate, with RR 37.8% (2.4% complete response and 35.4% partial response), 6 month progression free survival rate, PFS6 (50.3%) and OS (8.7 months) [1].
Material and Methods: The data reported from our center the last 8 months show better results than those obtained in historical series in terms of complete response, but with bad tolerance. All the patients were older than 18 years, with refractory high grade glioma, histologically proven, and were treated with Bevacizumab in Combination with CPT-11.
Results: We have treated 6 patients (3 women and 3 men) with an average of 52.8 years (range 44−66). There were 4 primary glioblastoma, 1 anaplasic astrocytoma and 1 gliosarcoma. The performance status (PS) was excelent in 3 patients (0−1) and in the other 3 patients was 2.
The PFS 6 was 33.3% (n = 2). The overall response rate was 33.3% (n = 2). There were 2 complete response. The median number of infusion received was 3.6 (1−18). Lower doses of corticosteroids were needed in 3 patients. (50%).
In general there was no good tolerance to Bevacizumab. Two patients died due to a bowel perforation and one had a serious respiratory infection. All of them had a PS 2.
Conclusions: Based on retrospective data from our study, we support the use of CPT-11 Bevacizumab in recurrent malignant high grade gliomas, but it is important to explain the risk of serious secondary effects and to select patients.

References

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8754 POSTER

Discovery of a New Class of Microtubule Binding Drugs Which Significantly Affect the Viability and Transformation of Human Glioma Stem Cells

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Background: Gliomas are the most common primary brain tumours. Despite current treatments by surgery, radiation and temozolomide (TMZ), the median survival for patients diagnosed with malignant gliomas is still below two years. Within the tumour mass, resides glioma stem cells, which exhibit seminal properties of therapeutic resistance leading to tumour re-growth, and hence death of the patients. In this study, the ineffectiveness of current therapies prompted us to identify and characterize new classes of microtubule binding drugs in our effort to improve the survival of patients with this deadly disease.
Methods: We subjected a panel of human glioma stem cell line pre-clinical models to a wide variety of cancer assays, including viability/proliferation, cell death, cell cycle regulation, invasion, and transformation assays.
Results: Using a chemical genetic screen of microtubule binding drugs, which are derivatives of opium alkaloids, we identified new classes of compounds having profound inhibitory effects on the growth of human glioma stem cells, and with little or no toxicity on non-transformed cells. Glioma stem cells treated with our drugs succumb to significant cell cycle arrest and apoptosis, which subsequently causes profound decreases in viability, proliferation, migration and even transformation. Further testing reveals that these drugs also enhance the radiosensitivity of glioma stem cells.

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