P08.65 EVALUATION OF CLINICAL BENEFIT IN PATIENTS TREATED WITH BEVACIZUMAB

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OBJECTIVE: Bevacizumab (BV), a monoclonal antibody for the treatment of recurrence of glioblastoma, was approved in 2009 in USA whereas today no such approval there is in the European Union. BV showed a higher response rates and prolongation of median at 6 month progression free survival (PFS) compared with historical treatment. The aim of this study was to evaluate the clinical benefit (CB) of BV therapy alone or in combination in the treatment of recurrent glioma (RG).

METHODS: Data of RG patients treated with BV alone or in combination treated in two Italian Center (National Cancer Institute Regina Elena of Rome and Department of Clinical and Experimental Oncology of PADUA) since 2012 were collected. CB was evaluated measuring reduction of steroid and improvement of Karnovsky Performance Status (KPS) of at least 20 point.

RESULTS: We enrolled 138 RG treated with BV. Of them 32 are female (37%) and 86 are males (63%). The majority of patients were glioblastoma (N=112, 91%) previously treated with three lines of chemotherapy before BV (N=103). At enrollment 113 patients was receiving steroid. 60% of patients showed reduction of steroids dose (in 94% after the first infusion of BV). A CB was observed in 62% of patients without significant differences between patients treated with BV alone or in combination. Also 27 patients with a progression disease at MRI showed a CB in 42% during the treatment. Patients with a CB showed a rate of progression free survival (PFS) at 1 year of 17.6%, significantly higher (p=0.0001) than patients without CB. Also OS resulted significantly different (p=0.0009) between group with CB (rate of OS at 1 years 37.9%) respect patients without CB 14.1%.

DISCUSSION: In this study the majority of patients treated with BV reported a clinical benefit, even in those showing radiographic progression. Moreover, patients with clinical benefit showed a better rate of progression free survival at 1 year and a longer survival. Our results confirm the role of BV in the treatment of recurrent glioma and the favourable impact on patients clinical symptoms.

P08.66 THE NS1 GlioBLASTOMA MODEL

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One of the key problems when treating patients with malignant gliomas is that despite being able to remove the major bulk of the tumour, tumour cell migration extends far beyond the resection margin. Therefore, a good model is needed to study the key components of the Ran pathway in astrocytomas and a further increase of RCC1 increased in primary and secondary glioblastoma recurrent tumours after radiotherapy led to further enhanced expression in primary and secondary glioblastoma, in particular after cisplatin treatment. Peritumoral brain tissue was used as a negative control of patient tumours.

RADIOCHEMOTHERAPY

INTRODUCTION: Numerous studies on different non-brain cancers indicate that many of these tumours have infiltrative growth patterns and can be investigated directly under fluorescence microscope. Tumour cells can be used in fully immunocompetent animals, which is otherwise a problem when researchers want to combine GFP-expressing tumour cells and immunotherapy studies.

P08.67 INHIBITION OF MUTT HOMOLOG 1 (MTH1) IN GlioBLASTOMA MULTIFORME RESULTS IN IMPAIRED CELL MIGRATION AND TUMOR GROWTH

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INTRODUCTION: MutT homolog (MTH1) is required for survival of cancer cells. These have irregular redox formation resulting in the production of reactive oxygen species which damage the deoxynucleoside triphosphate pool and subsequent the DNA. MTH1 plays a crucial role by inhibiting the incorporation of oxidized bases into the DNA that avoid apoptosis of cancer cells. Our aim was to analyze the pathophysiological role of MTH1 in glioma.

MATERIALS AND METHODS: MTH1 expression was analyzed in human glioma specimens by quantitative RT-PCR, immunohistochemistry and Western Blot. U87 cell migration in vitro and tumour growth in an orthotopic rat model was monitored after knock-down of MTH1 by siRNA or inhibition by crizotinib. In addition, progression free survival of patients was correlated to the MTH1 level.

RESULTS: Higher expression of MTH1 was observed in glioblastoma than in lower grade astrocytomas (p<0.05) and peritumoral tissue, both, on the gene and protein level. MTH1 siRNA transfected U87 cells showed slower migration compared to control U87 cells (p<0.01). Furthermore, treatment with crizotinib, an inhibitor of MTH1, also lowered cell migration. In rats, tumour growth was significantly impaired in MTH1 siRNA U87 grafts (p<0.01).

DISCUSSION: These results show that MTH1 might play an essential role in both, malignantization of glioma and disease progression in recurrent glioblastoma. Moreover, the MTH1 level in patients seems to influence tumour growth and could be targeted by crizotinib indicating a role for potential future therapies.

P08.68 THE RAN SIGNALING PATHWAY IS UPREGULATED DEPENDENT FROM GLIOMA GRADE AND RADIOTHERAPY


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INTRODUCTION: Several studies have shown that the Ran signalling pathway in astrocytoma, we measured the expression of its key components Ran, RCC1, RANBP1 and RANBP2 in different types of brain tumour tissue.

MATERIALS AND METHODS: Using qRT-PCR and Western blot analysis the expression of the gene and protein expression was analyzed in 80 tissue samples. The tissue subtypes were astrocytomas WHO II, anaplastic astrocytomas, primary and secondary glioblastomas and tissue samples after recurrence subsequent to radiochemotherapy. Pertumoral brain tissue was used as a control. For PCR analysis at least 10 glioma probes and for Western blot analysis at least 6 glioma probes were used per group.

RESULTS: Ran protein overexpression compared to non-neoplastic brain was detected in anaplastic astrocytoma (90%), primary glioblastoma (140%) and secondary glioblastoma (170%). With increasing WHO grade there was an increase of Ran mRNA expression and chemoradiation therapy led to further enhanced expression in primary and secondary glioblastoma after radiochemotherapy from 3.16 to 2.25 and from 2.08 to 3.08 arbitrary units (AU), respectively. There was also an increase in gene expression of RCC1, RANBP1 and RANBP2 analogue to that of Ran: showing a steady increase with higher WHO grading. Correspondingly to Ran, gene expression of RCC1 increased in primary and secondary glioblastoma after radiochemotherapy from 3.19 to 3.87 AU and from 4.14 to 10.11 AU respectively as well as that of RANBP2 from 2.36 to 5.14 AU and from 2.77 to 4.74 AU respectively.

DISCUSSION: Our data clearly show a grade dependent upregulation of key components of the Ran pathway in astrocytomas and a further increase after radiochemotherapy. Therefore, this pathway may represent a future target for glioblastoma therapy.