EP-0997

Polymorphisms of Akt and EZH2 as predict factor of radio-chemotherapy in patients with glioblastoma (GBM)

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Purpose/Objective: GBM is most common primary brain tumor and represents an important challenge for clinicians. These neoplasms are resistant to radio-chemotherapy. This might be explained by the fact that interactions between tumor and microenvironment are involved in tumor radioresistance through angiogenesis, hypoxia and immunosuppression, or an intrinsic radioresistence of cancer stem cells. A molecular analysis in tumor samples or peripheral blood of basal activation of different signaling pathways potentially involved in radioresistance could be of clinical interest. Phosphatidyl-inositol 3-kinase/protein kinase B (Akt) pathways serve to block apoptosis, keeping cells alive in very toxic environments such as chemotherapy and ionizing radiation. Polycomb group (PcG) proteins mediate gene silencing through histone post-translational modifications. PcG function is crucial for neural stem cell self-renewal. Recent evidence indicates that PcG genes are also required for cancer stem cell (CSC) propagation in neural tumors. In this study we evaluated the different genetic profile of Akt and EZH2 and clinical response to treatment in patient affected by GBM.
Materials and Methods: Our plan is to analyze fifty patients with GBM treated with Radio-chemiotherapy (RT-CT) with temozolamede. Time to progression (TTP) after surgery or biopsy and overall survival (OS) will be used as clinical end-points to be correlated with polymorphisms of Akt and EZH2. DNA is extracted by proteinase K digestion. SNP genotyping was performed with the ABI PRISM 7900HT Sequence Detection System using primers and probes designed with Methyl Express software (v. 1.0). DNA samples (1-20 ng) from cancer tissue were amplified l multiplex Real-Time PCR. In addition, by quantifying themin a 25- fluorescent signals of the VIC and FAM probes, which specifically annealed to the two allelic sequences, the SDS software (v. 2.1) determined the allelic content of each sample. For the Quantitative Methyl Specific PCR, the Bisulfite treatment of DNA was performed using the Methyl SEQr Bisulfit system according to manufacturer's protocol. Following bisulfite treatment, the converted DNA was amplified using primers designed for the altered sequences.
Results: preliminary data is available for ninenteen patients for polymorphisms of Akt after a follow-up of three – thirty-six months. The Akt1*3 wild-type genotype was detected in 12/19 of samples and the heterozygous genotype was found in 7/19. We also evaluated Akt1*4 polymorphisms, and the only 2 patients that showed mutant genotype had the longest survival time. The same analysis will be performed in 42 peripheral blood in pts underwent to the same treatment for GBM, findings will be available for the ESTRO meeting in May.
Conclusions: This study is currently ongoing, we actively accruing new cases and we are waiting for the data of peripheral blood. This preliminary analysis appears to indicate allelic discrimination of SNP's is a senstive and reproducible method. The screening of cell line genotypes may add to the prognostic value of histopathology samples.

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Conformal radio- and chemoradiotherapy in the management of high-grade glioma patients

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Purpose/Objective: Evaluation of 5-year treatment outcomes in high-grade (grade III-IV) brain glioma patients administered conformal radio-(chemoradio)therapy.
Materials and Methods: The study included 261 patients 22-74 years of age with Karnofsky perfomance scale of ≥ 50%. Fifty-four of them had pathological diagnoses of grade III anaplastic astrocytoma (AA), 17 - grade III anaplastic oligoastrocytoma or grade III anaplastic oligodendroglioma (AO/AOD), and 190 - grade IV glioblastoma (GBM). In 2005 - 2010, 114 of them received a course of postoperative conformal radiotherapy at a single target dose of 1.8-2 Gy up to total target doses (TTD) of 54-60 Gy, and 147 patients in 2007 - 2011 underwent a postoperative course of conformal chemoradiotherapy with temozolomide 75 mg/m^2 an hour before radiation treatment during the first and the last 2 weeks of radiotherapy at the same doses. The patient survival was evaluated using the data of Belarusian Cancer Registry as of November 15, 2012 and calculated with Kaplan-Meier method using the log-rank test and SPSS Statistics v.17 software.
Results: For the time being, 30 (55.6%) of 54 AA patients, 12 (70,6%) of 17 AO/AOD patients and 34 (17,9%) of 190 GBM patients are followed up. The median survival and 2-, 3- and 5-year survival rates for grade III gliomas are 33 months, 71.7±5.7%, 48.3±7.5% and 39.1±8.5%; for grade IV GBM - 14 months, 22.6±3.2%, 11.2±2.7% and 7.9±2.9% respectively (p<0.0001). The median survival of patients administered chemoradiotherapy for grade III glioma has not been attained yet, 3- and 5-year survival rates are 66.9±11.1%; the median survival of patients receiving radiotherapy is 29 months, and 3- and 5-year survival rates are 36.8±8.9% and 27.6±8.8% respectively (p=0.034). For GBM treated with chemoradiotherapy, the median survival and 2-, 3- and 5-year survival rates are 16 months, 25.2±4.7%, 11.1±3.9% and 7.4±4.0%; with radiotherapy - 12 months, 18.3±4.3%, 9.8±3.3% and 8.4±3.1% respectively (p=0.035). The median survival for AO/AOD was higher then for AA and was 46 months and 29 months respectively (p=0.069).
Conclusions: Postoperative conformal radio-(chemoradio) therapy at a TTD of 54-60 Gy provides 2-, 3- and 5-year survival rates of 71.7±5.7%, 48.3±7.5%, 39.1±8.5% and 22.6±3.2%, 11.2±2.7%, 7.9±2.9% for grade III anaplastic glioma patients and grade IV GBM patients respectively, with median survival of 33 and 14 months respectively (p<0.0001). Postoperative conformal chemoradiotherapy improves treatment outcomes compared with radiotherapy for both anaplastic gliomas (p=0.034) and GBM (p=0.035).

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Re-irradiation ± bevacizumab in recurrent or progressive HGG: retrospective analysis of 13 patients

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Purpose/Objective: To review the safety and activity of radiotherapy with concurrent bevacizumab in recurrent malignant gliomas. Reasons to combine bevacizumab and RT include the ability of antiangionetic agents to senzitize tumor endothelium to RT by depletion of VEGF and reduction of its pro-survival signaling. Our retrospective analysis provides additional data out of a very limited number of studies about safety and feasibility of conventionel 3D-conformal re-irradiation in combination with bevacizumab as a salvage therapy for relapsed gliomas.
Materials and Methods: Patients with recurrence of malignant gliomas who failed after standard treatment odf surgery, post operative radiotherapy ± Temozolomide received bevacizumab (10 mg/kg i.v.) every two weeks until tumor progression and hypofractionated (16 x 2.66 Gy). The intervall between the two radiotherapy treatments was at least 4 months in our patients. The median physical doses of the first and second radiation course were 40-60 Gy and 39-60 Gy, respectively. The median cumulative biological equivalent doses (BED) were 215 Gy (α/β = 2 gy) and 100 Gy (α/β = 10 Gy): Median RT-volume was 143 cm^3 and median cumulative RT-dose was 95 Gy.
Results: 13 consecutive patients with reccurrent malignant gliomas (6 GBM, 3 AAC, 3 LGG, 1 not applicable) received 2 cycles of bevacizumab prior to re-irradiation and underwent a repeat cranial MRI-scan for RT-planing. Patinets who respond or had SD proceed to radiation therapy in a 3D-conformal manner to 16 x 2.66 Gy: PTV inclosed the contrast-enhancing GTV, the surroundig oedema plus a additional margins of 2.5 cm. Critical structures like the optic chiasm were excluded and the dose to the re-irradiated target volume was restricted to a cumulative dose of 110 Gy. No Grade 3-4 acute toxicity developed, haematologic and non haematologic toxicities were transient. Until now 1 necrosis is seen in this cohort and all patients responded to therapy. The median PFS after re-irradiation is 4.9 months, the median OS after re-irradiation is 8.2 months.
Conclusions: 3D-conformal re-irradiation ± bevacizumab is save with a good quality of life for progressive HGG patients. The large re-irradiation volumes were well tolerated with a low rate of one confirmed radiation necrosis in 13 patients. Pretreatment with radiochemotherapy (temozolomide) does not increase neurotoxicity. The PFS is comparable to more complex and less abundant high precission radiation techniques.

EP-1000

Use of MRI diffusion-weighted images for follow up assessment of radiosurgery effectiveness for meningiomas.

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