
A subset of patients with recurrent high-grade gliomas benefits from the anti-angiogenic therapy bevacizumab (BVZ). An increased number of research efforts are performed to develop predictive biomarkers that allow for screening of patients. The immune system plays a crucial role in angiogenesis inhibition and maintenance. We analysed circulating immune cells in recurrent high-grade glioma patients treated with BVZ (10 mg/kg every 2 weeks) during a prospective bi-centric trial. Blood samples were collected before cycles 1, 3, 5 and 7 to perform flow cytometry analysis. A set of mononuclear-classical/immunomodulatory-cell markers (CD2/ VEGFR1+), Myeloid-Derived Suppressor Cells (MDSC) and regulatory T cells (Tregs) as well as a complete blood count. Thirty patients (29 GliaBlasts, 1 anaplastic astrocytoma) were enrolled between September 2012 and January 2014. Median OS and PFS were 9.1 months (6.7 – 18.4) and 3.5 months (1.8 – 5.1) respectively. During treatment results demonstrated a statistically significant increase in the median values of leukocytes, neutrophils, eosinophil, total and classical monocytes, as well as a statistically significant decrease of the percentage of Tregs among leukocytes. The strongest correlation between baseline levels of immune cells and OS was observed for neutrophils and Tregs. Patients with a percentage of Treg among leukocytes above the median (0.21%) had a higher OS (19.8 [17.5–na] versus 5.8 [6.7–12,2]) and PFS (HR: 0.13 p<0.001) compared to baseline neutrophil count (< 3.8 G/L) was associated with a better OS (17.5 [12.2–na] versus 5.3 [3.3–10.1] months, HR: 0.27p<0.002). Therefore, the detection of these cellular populations could provide insight into which patients may benefit from BVZ treatment. 1

P06.14 EARLY BIOMARKERS FROM CONVENTIONAL MRI AND TRAMS FOR PREDICTING RESPONSE TO BEVACIZUMAB IN RECURRENT HIGH-GRADE GLIOMAS
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PURPOSE: We have recently applied a novel technique, in which high resolution treatment assessment maps (TRAMs) are calculated from MRIs acquired with a delay of 2-3 hr, enabling efficient separation between tumor (contrast clearance >1 hr post injection) and treatment-effects (contrast accumulation) with no overlap. The TRAMs have been applied to study 320 patients with primary and metastatic brain tumors and have been validated histologically in 54 resected patients reaching 100% sensitivity and 93% positive-predictive value to active tumor. Here we studied the ability of the TRAMs over standard/advanced MRI methodologies in recurrent high grade glioma (rHGG) patients treated with bevacizumab; further, we determined MRI-based response/progression patterns and defined predictors of response for clinical decision making.

METHODS AND MATERIALS: 24 rHGG patients were studied before/ during bevacizumab treatment by standard/delayed-contrast MRI. A unique, semi-automatic segmentation algorithm was developed to enhance sensitivity to subtle enhancement on T1-Gd.

The TRAMS, previously shown to efficiently depict rHGG patients. During bevacizumab treatment by standard/delayed-contrast MRI. A unique, semi-automatic segmentation algorithm was developed to enhance sensitivity to subtle enhancement on T1-Gd. The TRAMS, previously shown to efficiently differentiate tumor/non-tumor tissues in brain-tumor patients undergoing conventional treatments, were calculated from delayed-contrast MRIs. The patients were divided into responders (overall-survival (OS)/2 year) and non-responders (OS<1 year). The changes in lesions volumes one month after treatment initiation, calculated from standard/delayed-contrast MRIs, were studied as potential predictors of outcome using log-rank analysis and ROC analysis.

RESULTS: Seven patients were responders and seventeen non-responders. Response/Progression patterns were identified from the mean change in lesion volumes, depicted from conventional T1-Gd, delayed contrast MRI and DSC-MRI. Thresholds for early prediction of response were calculated using these sequences. Sensitivity/specificity/positive-predictive value/negative-predictive value were calculated for each predictor, reaching 100%/87.5%/77.8%/100% for TRAMS, 85.7%/87.5%/75%/93.3% for T1-Gd and 75%/78.6%/50%/91.7% for PWL. The benefit of the TRAMS in separating responders/non-responders was further confirmed using log-rank analysis (T1-Gd: p=0.002, TRAMS: p=0.0001, PWL: p<0.02). ROC analysis demonstrated the added value of the TRAMS for prediction of 6 months PFS and 1 year OS. At progression, the increase in lesion-volumes in the TRAMS was 37.5% higher than the increase in conventional T1-Gd (p<0.001), suggesting progression may be depicted more effectively in the TRAMS.

CONCLUSIONS: The benefit of MRI for assessing and predicting response to bevacizumab was demonstrated. The TRAMS increased sensitivity reflects their potential contribution to management of bevacizumab.

P06.15 IFI16 EXPRESSION IN GLIOMAS AND ITS POTENTIAL ROLE IN IMMUNOSURVEILLANCE
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In glial tumors the immune-escape is an important mechanism to promote invasion and aggressiveness, thus the aim of our study was to investigate the expression of Interferon inducible protein 16 (IF16) in human gliomas. IF16 is a member of the p200 human family proteins that are highly conserved repeats at C-terminus which allow them to bind dsDNA and is a typical protein-protein interaction domain at their N-terminus. IF16 gene is located at 1q23.1 chromosome and encodes for three isoforms of IF16: its functions ranging from transcriptional regulation, apoptosis, cell growth regulation and differentiation. Moreover, the role of IF16 in the immunomodulation of innate and adaptive immunity, IF16 protein is located in the nucleolar compartment where it is able to activate and fine-tune the transcription, while when it is located in the nucleoplasm is probably inactive. We have studied IF16 expression in 120 gliomas (40 grade II, 40 grade III and 40 glialomas) by immunohistochemistry, using two antibodies against the C- and N-terminus, and molecular biology techniques. All these cases were also evaluated for p53, IDH1/R132H, MGMT methylation status and 1p19q co-deletion status. Our results showed a strong nuclear expression of IF16 in astrocytic lower grade gliomas and this expression was strictly related to p53 nuclear expression: this co-localization was demonstrated by confocal analysis and suggests a role of IF16 and tumor suppression. In grade III gliomas and glioblastomas, IF16 was mostly expressed in the nucleoplasm: this shift to the inactive form is related to a shorter survival suggesting a role as prognostic factor. In oligodendrogliomas IF16 expression was completely absent and it is strictly related to 1p19q co-deletion, but with inter-IF16 gene, as showed by array-CGH analysis. As a final point, we have characterized tumor inflammatory infiltrates using antibodies against CD3, CD4, CD8, CD68 and FoxP3 related to IF16 expression and tumor survival. Particularly in glioblastomas we observed a major expression of CD3+CD4+ T cells and a unique, recurrent pattern in the cases with strong nuclear IF16 expression and shorter survival: while CD3+/CD4+ cells were present in glioblastomas with nuclear expression and longer survival, with also a strong activation of both microglia and macrophages, suggesting an inverse role of IF16 in immune modulation. In conclusion, this is the first study of IF16 in gliomas, and we identify IF16 as a new potential prognostic factor, highlighting its early role in proliferation, malignant progression and immunomodulation of these tumours.

P06.16 EGFRVIII AND 1P19Q CO-DELETION CAN CO-EXIST IN GLIOMAS
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INTRODUCTION: The co-deletion of complete chromosomes arms 1p and 19q is the hallmark of oligodendroglioma and is related to a favorable clinical outcome. The epidermal growth factor receptor (EGFR) is over-expressed in almost half of glioblastoma multiforme (GBM) and the most common EGFR mutant is EGFRVIII. EGFRVIII expression is an independent and significant unfavorable prognostic factor of survival. EGFRVIII and 1p19q co-deletion rarely co-exist in the same glioma tumor sample.

METHODS AND MATERIALS: We present two cases of GBMs, characterized by 1p19q co-deletion and the expression of EGFRVIII. In the first one, EGFRVIII was detected by immunohistochemistry (IHC) and in the second one with real time PCR in tumor RNA. 1p19q co-deletion was detected in both cases with DNA analysis (MLPA) of the tumor. Because of the rarity of this coexistence a “deeper” study of the molecular profile of these tumors will be undertaken with next generation sequencing and presented at EANO.

RESULTS: The first patient is a 51yo woman presumably diagnosed with glioblastoma grade IV with an oligodendroglioma component in August 2015. The patient was operated and then concurrent radiation therapy and temozolomide were given. She is now on adjuvant therapy with temozolomide. DNA analysis on tumor sample revealed 1p19q co-deletion and immunohistochemistry undertaken to evaluate her eligibility for the Rindo pepimut compassionate use program, revealed EGFRvIII mutation.

The second patient is a 39yo man diagnosed with GBM with an oligoden- droglioma component in March 2014. He was operated and subsequently treated with temozolomide and radiation therapy. Then, adjuvant temozolomo- lide was administered. In February 2015, a recurrence was detected, he underwent a re-operation and the same histological type was revealed. Treatment with bevacizumab and temozolomide was administered for 9 cycles. In November 2015 a new recurrence led to another operation. The tumor this time was described as a grade II/III oligodendroglioma. DNA analysis revealed that the tumor is informative for 1p19q co-deletion and it is

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