AI-29. ANGIogenic SWITCH FROM VEGFR2/HIF1α IN NEWLY DIAGNOSED Glioblastoma (GB) TO CXCR4-SDF1 Pathway In Recurrent Paired Tumor After Radiotherapy (RT)-Temozolomide (TMZ)

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BACKGROUND: Angiogenesis is one of the key features of GB. Our objective was to explore the potential changes of angiogenic factors expression between initial diagnosis of GB and recurrence after RT/TMZ.

METHODS: Paired frozen tumor tissues from both initial and recurrent surgery were available for 29 patients with GB treated with RT/TMZ without bevacizumab upfront. Screening of over 150 genes expressions related to angiogenesis was performed on first 10 paired samples, using RT-PCR arrays (Qiagen®). Comparative expressions were determined using Qiagen® software. In a second step, RNA expressions of the selected identified genes were analyzed on all samples (29 paired tumors) using quantitative RT-PCR (qRT-PCR). Protein expression was examined by immunohistochemistry (IHC) with a semi-quantitative measure. Anti-tumoral effect of an anti-CXCR4 (AMD3100) in addition to TMZ and RT was tested in GB explants.

RESULTS: In the screening step performed by RT-PCR arrays the initial-recurrence expression changes contributed to a selection of seven genes for which expression was then quantified by qRT-PCR: VEGFA, VEGFR2, VEGFR1, SDF1, CXCR4, uPA and HIF1α. From initial diagnosis to recurrence RNA expressions of CXCR4 (p = 0.029) and SDF1 (p = 0.107) were increased while expressions of HIF1α (p = 0.009) and VEGFR2 (p = 0.081) were decreased. Similarly, SDF1 protein expression (IHC) tended to increased (p = 0.096) while VEGFR2 staining was significantly decreased (p = 0.004) at recurrence. The role of CXCL4 was further supported by an increase of anti-tumoral effect observed with the combination of AMD3100 and RT/TMZ versus RT/TMZ alone in GB explants. By multivariate analysis, VEGFR2 RNA initial and recurrence expression levels were significantly correlated respectively to initial overall survival (p = 0.019, Hazard ratio (HR) = 3.650) and recurrent overall survival (p = 0.024, HR = 2.536).

CONCLUSION: Recurrence of GB after chemo-radiation could be associated with a switch of angiogenic pattern from VEGFR2-HIF1α to SDF1-CXCR4 pathway, leading to new perspectives in angiogenic modulation and GB treatment.