ASSOCIATION OF MATRIX METALLOPROTEINASE 2 (MMP2)
BASELINE PLASMA LEVEL WITH RESPONSE AND SURVIVAL
AND CHANGE OVERTIME IN PATIENTS TREATED WITH
BEVACIZUMAB FOR RECURRENT HIGH GRADE GLIOMA
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BACKGROUND: Predictive marker of bevacizumab activity is an unmet
medical need. We evaluated predictive value of selected circulating prebio-
markers involved in neoangiogenesis and invasion on patient outcome in recur-
rrent high grade glioma (HGG) treated with bevacizumab. METHODS: A set of
eleven prebiomakers of interest (VEGF, VEGF-R2, bFGF, SDF1, PlGF, uPA,
PAI1, MMP2, MMP7, MMP9, and adrenomedulline) were analyzed in
plasma, using ELISA, at baseline and 2 weeks apart from bevacizumab initia-
tion in a prospective cohort of 26 patients (Cohort1). Correlations were validated in a
separate retrospective cohort (Cohort2; n = 50) and tested in cohort patients
with cytotoxic agents without bevacizumab (Cohort3;n = 34).
Dosages were correlated to objective response (OR), Progression-free survival
(PFS), and overall survival (OS). In cohort 1, multiple time points were performed up to progression. Additionally MMP2 and MMP9 plasma levels were analyzed in patients with newly diagnosed GB, after surgery. Finally, MMP2 and 9 RNA were assessed in tumor tissue of a separated group of paired newly diagnosed and recurrent GB (n = 29). RESULTS: In cohort1, high MMP2 baseline level was associated to a probability of OR of 83.3% versus 15.4% in case of low MMP2 level (p = 0.001). In multivariate analysis, baseline level of MMP2 correlated with PFS (hazard-ratio(HR), 3.92; 95% confidence-interval(CI):1.46-10.52; p = 0.007) and OS (HR, 4.62; 95%CI
1.58-13.53; p = 0.003), as decrease of VEGF (p = 0.038 for PFS and p =
0.013 for OS) and MMP9 (p = 0.016 for PFS and p= 0.025 for OS). In
cohort2, MMP2, but not MMP9, confirmed its predictive significance. In
cohort3, no association was found between MMP2, MMP9 and outcome.
In cohort 1, significant changes in MMP2 and MMP9 plasma levels were observed during treatment. MMP2 increased after Bev initiation (p = 0.002), and decreased at progression (p = 0.002) while MMP9 initially decreased (p = 0.007) then increased at progression (p = 0.031). No significant difference was observed both for plasma level and tissue RNA expression between newly diagnosed and recurrent GB. CONCLUSIONS: In patients with recurrent HGG treated with bevacizumab, but not with cytotoxic agent, high MMP2 plasma levels are associated with prolonged tumor control and survival, while changes over time may reflect tumor control. Comparison of MMP2/MMP9 levels between initial diagnosis and recurrence may suggest that bevacizumab could be similarly effective in this two setting. MMP2 should be tested in ran-
donized clinical trials that evaluate bevacizumab efficacy, and its biological role reassessed. SECONDARY CATEGORY: Clinical Neuro-Oncology.