Dianhydrogalactitol (VAL-083) reduces glioblastoma tumor progression in vivo, upon bevacizumab-induced hypoxia

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Standard-of-care for glioblastoma (GBM) includes surgery, radiation and temozolomide. Nearly all tumors recur and 5-year survival is less than 3%. Unmethylated promoter status O6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for temozolomide-resistance. Second-line treatment with bevacizumab has not only failed to improve survival, but has also been shown to induce intratumor hypoxia and increased chemoresistance. VAL-083 is a bi-functional DNA-targeting agent that readily crosses the blood-brain barrier. VAL-083 targets N7-guanine, causing DNA double-strand breaks and cancer cell-death in GBM cancer stem cells (CSCs) and non-CSCs, independent of MGMT. To investigate the in vivo anti-tumor effect of VAL-083+bevacizumab, we used an orthotopic GBM T16 PDX model. All mice carried MGMT-unmethylated, temozolomide-resistant recurrent GBM tumors detected by MRI 35 days post-implantation. Tumor progression was measured by MRI on days 49 and 56, and was calculated for the entire study (day 35 vs. 56) and for the last 7 days (day 49 vs. 56). Mice were grouped into control, bevacizumab, VAL-083, and VAL-083+bevacizumab. VAL-083 treatment started 3 days after bevacizumab treatment to ensure induction of hypoxia. Results: Tumors were significantly smaller in VAL-083+bevacizumab compared to VAL-083 alone (p<0.01) and compared to bevacizumab-treated (-75%, p<0.001) in VAL-083-treated mice both compared to control (-83%). Unmethylated promoter status O6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for temozolomide-resistance. Second-line treatment with bevacizumab, VAL-083, and VAL-083+bevacizumab. VAL-083 showed increased TERT expression (34% and 14% respectively), and high percentage of TP53 and ATRX mutations. Multivariate analysis after adjusting for confounding factors including grade and age showed prognostic factors associated with survival (HR=3.2, p-value=0.001) in group 4 versus others. Conclusions: The results indicate that clinically relevant alterations exist within IDH-mutant gliomas that could stratify patients for treatment. Interestingly, group 4 showed high expression of HOX genes (18/18) (p-value=0.01) and higher methylation of Hox genes (21) (p-value=0.01) compared to others. Higher expression of specific Hox genes were associated with worse survival.

doi:10.1017/cjn.2018.301

Microglia and macrophages display heterogeneous phenotypes in IDH-mutant and -wildtype glioblastomas

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Background: CNS innate immune cells, microglia and macrophages (MMs), are the largest component of the inflammatory infiltrate in glioblastoma (GBM). They initially participate in tumor surveillance, but are subverted by GBM. Immunotherapies have proven incredibly successful in cancers...