ONCOLYTIC HERPES SIMPLEX VIRUS IMMUNO-VIROTHERAPY IN COMBINATION WITH TIGIT IMMUNE CHECKPOINT BLOCKADE TO TREAT GliOBlASTOMA

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Background Glioblastoma Multiforme (GBM) is an aggressive primary brain tumor and represents the most fatal type of malignant cancer. Despite rigorous clinical research efforts there is minimal improvement in GBM patient outcomes. Oncolytic herpes simplex virus 1 (oHSV-1) is emerging as a promising approach to promote anti-tumor responses in GBM patients. In this study, we hypothesized that intratumoral administration of a novel HSV-1 based oncolytic virus (HSV-1 rQNestin34.5v2) will result in synergy when combined with anti-TIGIT checkpoint blockade therapy. We investigated the antitumor efficacy of this combination in immunocompetent syngeneic murine glioma models that exhibit different genetic alterations and tumor mutations.

Methods HSV-1 based oncolytic virus (HSV-1 rQNestin34.5v2), currently investigated in a phase I clinical trial for recurrent glioblastoma (ClinicalTrials.gov: NCT03152318) was employed, that maintains a copy of the HSV-1- ICR34.5 gene, which is responsible for HSV-1 neurovirulence under transcriptional control of the tumor-specific promoter nestin to drive robust tumor-selective replication. Syngeneic GL261, CT-2A, IDH1 mutant and IDH1 wild type orthotropic glioma mouse models were used to evaluate immunotherapeutic and antitumor responses. Immune cell signatures at the tumor microenvironment and in the peripheral blood involved at the treatment response were assessed by multiparameter flow cytometry analysis.

Results HSV-1 rQNestin34.5v2 exhibited robust ability to infect murine glioma cells in vitro triggering cytotoxicity. Infection stimulated immunogenic cell death in glioma cells as evidenced by extracellular release of damage-associated molecular patterns (DAMPs) and proinflammatory cytokines. In vitro screens for upregulation of immune checkpoint molecules following infection with HSV-1 rQNestin34.5v2 identified CD155/CD112/TIGIT and PD-L1/PD1 axes as promising targets for combination therapies. TIGIT was found to be overexpressed in tumor infiltrating NK, CD4 and CD8 T cells suggesting systemic therapy with TIGIT blockade antibodies could have therapeutic utility in combination with HSV-1 rQNestin34.5v2 in GBM. Intratumoral administration HSV-1 rQNestin34.5v2 resulted in the development of a proinflammatory environment as shown by decreased CX3CR1 expression on tumor infiltrating NK cells. Benefit in overall survival was not observed by systemic anti-TIGIT monotherapy. Combination treatment with intratumoral HSV-1 rQNestin34.5v2 administration exhibited modest therapeutic effect with a cure rate 12% in mice bearing intracranial CT-2A tumors. Long term CT-2A tumor survivor mice were effectively protected by rechallenge with autologous CT-2A cells indicating the development of long lasting tumor specific immunity.

Conclusions Our findings show that the combination of HSV-1 rQNestin34.5v2 virotherapy with anti-TIGIT checkpoint blockade immunotherapy represents a promising strategy to overcome primary resistance to immune checkpoint inhibitors in GBM.

Ethics Approval All animal experiments and procedures described in this study were approved by Brigham and Women’s Institutional Animal Care and Use Committee.