Sci Transl Med. 2023 May 24;15(697):eadf2281. doi: 10.1126/scitranslmed.adf2281.
Epub 2023 May 24.

Targeted delivery of tumor necrosis factor in combination with CCNU induces a T cell–dependent regression of glioblastoma

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PMID: 37224228 DOI: 10.1126/scitranslmed.adf2281

Abstract

Glioblastoma is the most aggressive primary brain tumor with an unmet need for more effective therapies. Here, we investigated combination therapies based on L19TNF, an antibody-cytokine fusion protein based on tumor necrosis factor that selectively localizes to cancer neovasculature. Using immunocompetent orthotopic glioma mouse models, we identified strong anti-glioma activity of L19TNF in combination with the alkylating agent CCNU, which cured the majority of tumor-bearing mice, whereas monotherapies only had limited efficacy. In situ and ex vivo immunophenotypic and molecular profiling in the mouse models revealed that L19TNF and CCNU induced tumor DNA damage and treatment-associated tumor necrosis. In addition, this combination also up-regulated tumor endothelial cell adhesion molecules, promoted the infiltration of immune cells into the tumor, induced immunostimulatory pathways, and decreased immunosuppression pathways. MHC immunopeptidomics demonstrated that L19TNF and CCNU increased antigen presentation on MHC class I molecules. The antitumor activity was T cell dependent and completely abrogated in immunodeficient mouse models. On the basis of these encouraging results, we translated this treatment combination to patients with glioblastoma. The clinical translation is ongoing but already shows objective responses in three of five patients in the first recurrent glioblastoma patient cohort treated with L19TNF in combination with CCNU (NCT04573192).