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Fc-enhanced anti-CTLA-4, anti-PD-1, doxorubicin, and ultrasound-mediated BBB opening: A novel combinatorial immunotherapy regimen for gliomas

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Abstract

Background: Glioblastoma is a highly aggressive brain cancer that is resistant to conventional immunotherapy strategies. Botensilimab, an Fc-enhanced anti-CTLA-4 antibody (FcE-aCTLA-4), has shown durable activity in "cold" and immunotherapy-refractory cancers.

Method: We evaluated the efficacy and immune microenvironment phenotype of a mouse analogue of FcE-aCTLA-4 in treatment-refractory preclinical models of glioblastoma, both as a monotherapy and in combination with doxorubicin delivered via low-intensity pulsed ultrasound and microbubbles (LIPU/MB). Additionally, we studied 4 glioblastoma patients treated with doxorubicin, anti-PD-1 with concomitant LIPU/MB to investigate the novel effect of doxorubicin modulating FcγR expressions in tumor associated macrophages/microglia (TAMs).

Results: FcE-aCTLA-4 demonstrated high-affinity binding to FcγRIV, the mouse ortholog of human FcγRIIIA, which was highly expressed in TAMs in human glioblastoma, most robustly at diagnosis. Notably, FcE-aCTLA-4 mediated selective depletion of intra-tumoral regulatory T cells (Tregs) via TAM-mediated phagocytosis, while sparing peripheral Tregs. Doxorubicin, a chemotherapeutic drug with immunomodulatory functions, was found to upregulate FcγRIIIA on TAMs in glioblastoma patients who received doxorubicin and anti-PD-1 with concomitant LIPU/MB. In murine models of immunotherapy-resistant gliomas, a combinatorial regimen of FcE-aCTLA-4, anti-PD-1, and doxorubicin with LIPU/MB, achieved a 90% cure rate, that was associated robust infiltration of activated CD8+ T cells and establishment of immunological memory as evidenced by rejection upon tumor rechallenge.

Conclusion: Our findings demonstrate that FcE-aCTLA-4 promotes robust immunomodulatory and anti-tumor effects in murine gliomas and is significantly enhanced when combined with anti-PD-1, doxorubicin, and LIPU/MB. We are currently investigating this combinatory strategy in a clinical trial (clinicaltrials.gov NCT05864534).

Keywords: BBB; Fc-enhanced anti-CTLA-4; Glioblastoma; doxorubicin; immunotherapy.