

Combination Therapies: Innovative Approaches to Circumvent Glioblastoma Immune Evasion Tactics

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Editorial

Glioblastoma (GB) is the most common malignant primary neoplasm of the brain and 5 year survivals range from 1-5% [1,2]. Despite aggressive standard of care therapy, the median survival time for GB patients is approximately 12-15 months [3]. In addition to the highly invasive nature of GB, the cellular and genetic heterogeneity of GB is an obstacle in eliminating GB with current therapies. Supporting this notion, four recently defined molecular GB subtypes show unique genetic features and sensitivities to therapy [4]. Recent clinical data suggests some improvement in clinical endpoints with immune checkpoint inhibitors in treating glioblastoma.

The success of immunotherapy for GB might be limited by the immune tolerant properties of the brain and immune evasion mechanisms employed by GB. The brain was termed an "immune-privileged" organ since the brain shows a high degree of tolerance to allografts relative to other organs [5]. Barriers to the induction of pro-inflammatory events in the brain are traditionally noted to be the blood-brain barrier [6], low or absent expression of HLA class I molecules on brain cells [7,8], the absence of conventional lymphatic drainage [9] and the absence of resident dendritic cells [10]. The strict regulation of immune reactions ensures that the toxicity and rise of intracranial pressure induced by inflammation do not lead to neuronal death within functional regions of the brain. The threshold for inducing immune reactions in the brain is high, however there is clear evidence of anti-tumor responses [11]. Human gliomas show infiltration by T cells suggesting the induction of anti-tumor immune cell infiltration [12].

Tumor-specific T cells stimulated by immunotherapy need to circumvent an immunosuppressive milieu prior to exerting their anti-tumor activities. Secreted factors by normal brain cells such as VEGF and TGF- β inhibit T cell proliferation, T cell activation, and T cell-mediated tumor cell lysis [13,14]. Normal neurons express Fas-L that may induce apoptosis of infiltrating T cells [15]. Interestingly, GB cells themselves express Fas-L to "counter-attack" tumor-specific T cells [5]. GB uses various mechanisms to resist immune attack including down regulation of HLA class I molecules or induction of immunosuppressive molecules such as HLA-G and PD-L1 [5]. Moreover, brain tumors secrete immunosuppressive molecules such as IL-10, TGF- β and PGE2 [5] and they express IDO and TDO enzymes that inhibit T cell activity and survival by depleting the tumor microenvironment of L-tryptophan [5-16]. GB recruits Tregs and myeloid-derived suppressor cells that act as cellular shields to protect GB cells against CD8⁺ killer cells [5-17]. Given the obstacles posed by the unique immunological properties of the brain and the immune evasion strategies utilized by GB, researchers have been investigating

combination therapies to improve the chances of efficacy with different types of immunotherapy for GB.

Preclinical and clinical studies support the use of combination therapies to sensitize GB to immunotherapies [18-22]. The mechanisms of immunosensitization of GB cells with radiation and chemotherapy is the upregulation of Fas, HLA class I and pro-inflammatory molecules [21,22]. Ongoing clinical trials are exploring combinations of chemotherapy or radiation with CAR T cells and immune checkpoint inhibitors [23]. Immune checkpoint inhibitors such as anti-PD1 and CTLA-4 antibodies allow T cells to retain their anti-tumor activity and thereby promote a sustained tumor attack by T cells. Clinical trials using immune checkpoint inhibitor antibodies against PD1 and CTLA-4 are being conducted for recurrent or newly diagnosed GB [23]. CHECKMATE-143 studied nivolumab (anti-PD1 antibody) and ipilimumab (anti-CTLA-4 antibody) combination therapy or nivolumab monotherapy at first recurrence after radiation and temozolomide [23,24]. One patient in the nivolumab monotherapy arm had a partial response and approximately 50% of patients in the nivolumab monotherapy arm and in the nivolumab and ipilimumab cohort had stable disease. The final findings of CHECKMATE-143 are soon to be released. In other trials, the approach is a combination of immune checkpoint inhibitors with neutralizing antibodies to either TGF- β or IDO. The rationale is to promote vigorous anti-tumor T cell responses by preventing T cell exhaustion and removing the immunosuppressive microenvironment created by TGF- β and IDO [23].

Combinatorial therapies are being explored in GB treatment and offer promise for mitigating the immunosuppressive microenvironment. Simultaneous targeting of the immunosuppressive microenvironment may yield better therapeutic outcomes for GB patients relative to current monotherapy approaches.

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