Can patient selection and neoadjuvant administration resuscitate PD-1 inhibitors for glioblastoma?

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To date, glioblastoma (GBM) remains an incurable disease that ipso facto urgently needs novel therapies. Maximal resection followed by radio-chemotherapy typically yields temporary disease control, and whereas this leads to prolongation of overall survival (OS), the outcomes are still dismal.28,29 More recently, tumor-treating electrical field therapy was found to further increase the OS of these patients, reaching a new benchmark of 43% 2-year survival.30 Whereas these therapies show some efficacy in the upfront setting, nearly all patients ultimately experience recurrence of disease. Unfortunately, to date there are no treatments that prolong survival for recurrent GBM. Several clinical trials testing immune checkpoint inhibitors (ICIs) in GBM are ongoing. However, it is expected that if a benefit is noted, it may be for a limited subset of patients. Therefore, strategies to optimize patient selection and timing of therapy might provide a means for effective immunotherapy for these tumors.

Considerations for Interpreting PD-1 Blockade Trials in GBM

At the outset, ICIs targeting the PD-1 receptor on CD8+ T cells suggested an encouraging opportunity for GBM given the remarkable success and enduring clinical responses of 40%, 44.8%, and 66.3% seen in advanced metastatic melanoma, non–small cell lung cancer, and Hodgkin’s lymphoma, respectively.23,25,32 However, this benefit has not been observed in GBM. It was recently announced that the primary endpoint of OS was not met in the phase III clinical trial CheckMate-498, in which investigators evaluated nivolumab plus radiation versus temozolomide (TMZ) plus radiation in patients with newly diagnosed methylguanine methyltransferase (MGMT)–unmethylated GBM.6 Also, recent news announced that one of the primary endpoints, progression-free survival (PFS), was not met in the CheckMate-548 randomized phase III clinical trial evaluating nivolumab in combination with TMZ and radiation compared to TMZ and radiation in newly diagnosed MGMT-methylated GBM.7 Despite this result, the trial will continue to evaluate whether there is a benefit in OS. Earlier, the phase III CheckMate-143 trial demonstrated that adjuvant nivolumab monotherapy was not superior to bevacizumab monotherapy in prolonging OS of patients with recurrent GBM.22 Similarly, a randomized phase II trial of pembrolizumab alone versus pembrolizumab and bevacizumab in recurrent GBM revealed no significant difference in OS despite an expected improvement of 6-month PFS in the bevacizumab arm.21

Despite negative results of these trials, a few considerations must be kept in mind. First, approximately 40% of the patients treated with PD-1 blockade were simultaneously given steroids, including 14% who received 4 mg or more of dexamethasone per day.22 This is highly relevant given the immunosuppressive properties of dexamethasone, and the previous reports associating steroid intake with lack of response to immunotherapeutic modalities including PD-1 inhibition in cancers in which this therapy exhibits efficacy.2 Moreover, 8% of patients from the CheckMate-143 clinical trial exhibited response to PD-1 blockade defined by the objective response rate per Re-
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Neoadjuvant PD-1 Blockade and Molecular Determinants of Response in GBM

Lately, 3 different clinical studies have provided important insights about the timing of drug administration and tumor genomic profile associated with the efficacy of PD-1 inhibitors for GBM. An interesting concept explored in some of these studies is the administration of neoadjuvant therapy, which is defined as a medical treatment given prior to surgery. Neoadjuvant PD-1 blockade immunotherapy achieved heightened T-cell responses and an increase in OS in melanoma and resectable lung cancer. The rationale for administering ICIs before surgery relies on the presurgical priming of the immune system to induce a persistent response of tumor-specific T cells after surgery. The theoretical appeal of neoadjuvant immunotherapy relates to the presence of the tumor mass and associated exposure to tumor antigens for the expansion of tumor-specific T cells at the time of therapeutic PD-1 blockade. Accordingly, 2 studies evaluated neoadjuvant administration of PD-1 inhibition in recurrent GBM. Only 1 of these studies, a randomized controlled trial evaluating neoadjuvant pembrolizumab, showed an increase in OS of 6.2 months (95% CI 0.17–0.94; p = 0.04) and an increase in PFS of 0.9 months (95% CI 0.20–0.90; p = 0.03) compared to the use of adjuvant therapy in patients with GBM. Other ongoing studies involving neoadjuvant ICI (NCT02794883, NCT02337686) may help further elucidate this.

Neoadjuvant administration provided the possibility to investigate the effect of PD-1 blockade on tumor cells and the microenvironment. For instance, gene expression analysis revealed higher activation of interferon-gamma (IFNγ) response in the neoadjuvant group compared to the adjuvant group, including upregulation of the immunosuppressive genes CD274 (PD-L1) and IDO1 by tumor cells, supporting the rationale of adding an IDO inhibitor to PD-1 blockade. In the analysis of the randomized phase II trial, 21% (3 of 14) of patients receiving pre- and postsurgical nivolumab had enrichment of cell cycle/proliferation genes compared to 73% (11 of 15 patients) of the adjuvant group. Given the low number of patients with GBM, it was not possible to determine the effects of neoadjuvant PD-1 inhibition on CD8+ T-cell infiltration. However, the only cases with high CD8+ T-cell infiltration (> 2% of total cells) were in 2 patients from the neoadjuvant group. T-cell receptor (TCR) sequencing analysis in blood and tumor revealed an increase in tumor-specific TCR clones after surgery when giving PD-1 inhibitors in the neoadjuvant setting. This suggests that presurgical PD-1 inhibition induced a local and systemic immune response of tumor-specific T cells that was enhanced by tumor antigen exposure during surgery and was prolonged in subsequent postsurgical doses. Neoadjuvant approaches directly involve neurosurgeons for coordinating immunotherapy infusion prior to resection, as well as tissue procurement. Also, in the context of immunotherapy, perioperative dexamethasone can and should be avoided in patients who do not have symptoms related to vasogenic edema, because this might ultimately impair the response to this therapy. Overall, the study by Cloughesy et al supports an association between PD-1 inhibition in the neoadjuvant setting and a survival benefit. This study also provides a mechanistic insight into how PD-1 blockade might influence the tumor microenvironment and the proliferation of tumor cells.

In an additional clinical study, neoadjuvant nivolumab was tested in 3 primary and 27 recurrent GBMs requiring resection in a single-arm phase II clinical trial. The median OS and PFS of these patients were 7.3 months and 4.1 months, respectively. Compared with a historical series of patients with GBM treated with the conventional radiochemotherapy regimen, the group treated with nivolumab had increased expression of the adaptive immune cell chemokines CXCL10, CCL4, and CCL3L1, in addition to downregulation of C-reactive protein, SSX4, and complement receptor 2. Moreover, increased T-cell clonality was noticed in postsurgical GBM samples after neoadjuvant PD-1 inhibition. Along the same lines, the high clonal TCR diversity was shown to correlate with longer survival compared to a low TCR clonotype in patients with GBM who were receiving neoadjuvant nivolumab.

Some evidence also suggests that patient selection might play a role in the efficacy of PD-1 blockade for GBM. Our group characterized the genomic hallmarks associated with response to PD-1 inhibitors (nivolumab and pembrolizumab). We analyzed the genomic and clinicopathological features of recurrent GBM in patients treated with nivolumab or pembrolizumab. The patients were classified as responders or nonresponders by imaging (MRI) and pathological criteria. Responder patients had a median OS of 14.3 months versus 10.1 months of the nonresponder patients (p < 0.05). The analysis of whole exomes and transcriptomes revealed genetic alterations associated with response to ICIs. For instance, activating mutations in BRAF and PTPN11, members of the MAPK pathway, were found more frequently in the responder group (p = 0.019). On the other hand, PTEN mutations were more prevalent in the nonresponder group than in the responder group (p = 0.0026). It has long been known that loss of PTEN function has immunosuppressive effects in gliomas, such as increasing the protein levels of PD-L1. Our study suggests that this and other distinctive genetic features can help predict the response to ICIs in patients with GBM. Moreover, when performing gene enrichment analysis in these tumors, gene sets related to a regulatory T cell (Treg) expression profile were the most upregulated before PD-1