Immunotherapy for glioblastoma: are we finally getting closer?

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Considerable energy and resources have been devoted to developing effective immunotherapies for glioblastoma (GBM). Recent progress in both systemic cancers and GBM suggest that these efforts hold a great deal of promise. The latest immunotherapy approaches have improved patient survival, provided a greater understanding of antitumor immune mechanisms, and resulted in FDA-approved agents for an expanding number of malignancies. In this issue, Sampson et al present the results of their phase II multicenter trial using the rindopepimut vaccine in patients with newly diagnosed EGFRVIII-expressing GBM. Do these results bring us closer to a strategy for effectively using the immune system to improve outcome for GBM patients?

Recent immunotherapy trials have highlighted the importance of heterogeneity in the immune microenvironment, including wide variability in the degree of intrinsic immunogenicity exhibited by different tumors. For example, melanoma is highly immunogenic and responsive to immunotherapy,2 while prostate cancer appears to be more immunosuppressive and in turn less responsive to similar immunotherapeutic approaches.3 Historically, GBM has been placed on the suppressive end of the immunogenicity spectrum.4 The parenchyma of the brain is known to be immunosuppressive, and GBM (which originates from brain matter itself) has been shown to usurp mechanisms of immunosuppression inherent to the CNS.5 Furthermore, the immunosuppressive effects of GBM are not limited to its microenvironment. GBM also negatively alters peripheral immune function as evidenced by its capacity to induce expression of programmed death ligand 1 (PD-L1) in myeloid cells.6 However, the very notion of CNS immune suppression is being challenged and redefined. As an example, the leptomeninges possess the ability to generate T cells that are capable of spontaneous antitumor activity.7,8 We have come to appreciate that immunotherapy is possible in the CNS, with success likely dependent upon developing tumor-type and tumor-site specific approaches.

The peptide vaccine used by Sampson et al is based on the epidermal growth factor variant III (EGFRVIII), a protein discovered by Wong et al that is uniquely expressed on cancer cells including subsets of GBM.9 EGFRVIII is a constitutively activated receptor with a truncated extracellular domain that is immunogenic.9,10 Interestingly, EGFRVIII is expressed only in a minority of patients with GBM (~25%-30%) and is thought to be a negative prognostic indicator.10 The study currently reported by Sampson et al initially started as an open-label randomized trial. However, due to high attrition rates in the control arm, the trial was converted to a single-arm phase II trial. The investigators assessed the efficacy of the rindopepimut vaccine in newly diagnosed patients following tumor resection. Eligible patients were initially primed with 3 doses of vaccine after completion of standard chemoradiotherapy and were then treated indefinitely on a monthly basis. In total, 65 patients received the vaccine. The toxicity profile was favorable. Grade 3 or 4 events were minimal, and the most common adverse event was injection site reactions. Progression-free survival (PFS) at 5.5 months was 66%, median PFS was 9.2 months, and median overall survival (OS) was 21.8 months. As a control, the authors looked at the EGFRVIII-positive patients from the RTOG 0525 trial who matched the eligibility criteria for the ACT III trial. They reported that the median OS of the ACT III patients (21.8 months) was superior to the median OS of the matched RTOG 0525 patients (16.0 months).11,12 Patients with methylated MGMT also fared better in this study, consistent with this predictor of favorable response to standard therapy.10 Evidence for immune activation in response to the rindopepimut vaccine came from serologic analyses demonstrating increased anti-EGFRVIII antibody titers in the patient serum. In addition, 4 of 6 pathology samples were EGFRVIII negative in the patients who had undergone repeat tumor resection after recurrence. Attempts to quantify lymphocyte activity were unfortunately not possible due to low numbers of harvested T cells.10 Additional evidence for assessing rindopepimut vaccine efficacy is coming from the ReACT trial, which was recently presented at the Society for Neuro-Oncology Meeting (2014). This meeting presentation reported improved survival in patients with recurrent GBM who were treated with bevacizumab and rindopepimut vaccine versus bevacizumab alone. Patients in the bevacizumab and rindopepimut group reportedly developed anti-EGFRVIII antibodies, and their tumors lacked detectable EGFRVIII-expressing cells at recurrence.13 These promising results led to the recent FDA designation of rindopepimut as a breakthrough therapy.
Sampson et al have suggested that antitumor immune responses can be elicited against GBM despite its immunosuppressive features. Unlike other immunotherapies such as cytokine therapy or passive therapy, the rindopepimut vaccine activates the adaptive immune response by first activating antigen-presenting cells (APCs) at the site of the peptide vaccine injection. The APCs in turn travel to the lymph nodes to activate T cells. While they observed objective tumor responses, the proposed therapeutic mechanism based on specifically targeting EGFRvIII-expressing cells might be considered discordant with the biology of GBM. What is interesting is that the majority of tumor cells within a GBM are not EGFRvIII positive.14 Hence, the majority of tumor cells would not be targeted by cytotoxic immune cells directed at EGFRvIII. The authors appropriately note this apparent paradox and propose alternative mechanisms such as a bystander effect or the targeting of EGFRvIII-expressing GBM stem cells. Another explanation could be epitope spreading. By inducing an antitumor immune response against the EGFRvIII-positive cells, additional tumor antigens are exposed when these cells are killed. The immune system in turn uses these new antigens to generate a diverse array of effector cells to target the entire tumor.15 This trial also addresses an important question about how to integrate immunotherapy with the current standard of care. Temozolomide is known to cause lymphopenia, and studies suggest that lymphopenia is a negative prognostic indicator in patients with multiple cancers, including GBM.16,17 Hence, one might assume that chemotherapy would undermine immunotherapy’s efficacy. Preclinical studies are at best ambiguous and show that systemic chemotherapy can be either counterproductive or potentially synergistic in generating an immune response.18 However, other findings from Sampson et al show that temozolomide can enhance the antitumor immune response by reducing regulatory T cells in the setting of lymphopenia.19,20 These divergent results could be explained by differences in the chemotherapeutic agents or immunotherapeutic protocols employed. The inclusion of radiation as a component of vaccine-based therapy also raises similar questions since Grossman et al show that brain radiation also induces lymphopenia.16

As we await results from the phase III placebo controlled trial (ACT IV) evaluating the addition of rindopepimut to standard chemoradiotherapy in patients with newly diagnosed EGFRvIII-positive GBM, the findings of this current study are encouraging and raise many new interesting questions and challenges. This and other emerging immunotherapeutic approaches, such as dendritic cell vaccines and checkpoint inhibitors, are indicative of a new dawn of potentially effective therapies for patients with GBM.

Funding
Research Support: BMS, Arbor Pharmaceuticals, Aegerus, CellDex, Alt and Accuray.

Conflicts of interest statement. Consultant: BMS, Merck.

References