Viral Therapy for Glioblastoma: Lessons Learned From Contradicting Results

BY PATRICK WEN, MD, & TIMOTHY F. CLOUGHESY, MD

Glioblastoma (GBM) is the most common and aggressive brain tumor. Most patients diagnosed with GBM die of their disease within 2 years, and long-term survival is rare even after optimal surgical resection. Despite numerous efforts, very little improvement in survival has been made in the last decade, and several negative phase III studies were reported recently. Negative results in a phase III study often indicate that the drug is not efficacious and lead to the abandonment of further clinical development. However, this is not necessarily the only option. The medical community can benefit greatly from studying unsuccessful trials and implementing lessons learned from them.

In manuscripts accepted for publication by *Neuro-Oncology* (e-published Dec. 17, 2019), Cloughesy et al and Brenner et al describe a case of contradicting results in two studies that assessed VB-111 in GBM, and the conclusions that were made after analyzing possible reasons for the different results.

Ofranergene obadenovec (VB-111) is an anti-cancer viral gene therapy with a dual mechanism of action: vascular disruption of tumor’s blood vessels leading to tumor starvation and induction of a tumor-directed immune response (Figure 1). VB-111 is based on a replication-deficient adenoavir type 5 vector, which carries a transgene for a chimeric death receptor that is expressed only in angiogenic endothelial cells. The binding of TNFα to the receptor activates the FAS pro-apoptotic pathway and leads to tumor vessel disruption.

In addition, through mechanisms of viral immune-ology, VB-111 promotes specific intra-tumor activation of the immune system, seen by an increase in tumor-infiltrating CD8 cells, thereby turning “cold” tumors “hot” and inducing an antitumor immune response.

In a phase II study (NCT01260506), patients initially treated with VB-111 monotherapy priming, that was continued after disease progression in combination with bevacizumab, had durable tumor growth attenuation and a median OS time of 414 days, compared to 223 days in patients with limited exposure to VB-111 (HR 0.48 [95% CI 0.23-0.99]; p=0.043). The survival advantage was also apparent in comparison to literature reports of eight studies in rGBM, where 12-month overall survival (OS) with bevacizumab monotherapy was 24 percent compared to 57 percent in the VB-111 primed combination phase II (p=0.03). Responders to VB-111 showed characteristic MRI response of expansive areas of necrosis in the areas of initial enhancing disease. An example of this distinctive MRI response can be seen in Figure 2 that displays the MRI series of a patient with complete response following VB-111 monotherapy, who remains disease-free for over 5 years.

These results led to the GLOBE study (NCT01260506): a pivotal phase III randomized, controlled trial that compared the efficacy and safety of upfront combination of VB-111 and bevacizumab versus bevacizumab monotherapy. Patients in GLOBE were randomized 1:1 to receive VB-111 1013 viral particles IV q8W in combination with bevacizumab 10 mg/Kg q2W (combination arm) or bevacizumab monotherapy (control arm). Unfortunately, the study did not meet its primary or secondary goals. Median OS was 6.8 versus 7.9 months in the combination versus control arm (HR 1.20 [95% CI 0.91-1.59, p=0.19) and ORR was 27.3 percent versus 21.9 percent (p=0.26). Trends for improved survival with combination treatment were seen only in the subgroup of patients with smaller tumors and in patients who had a post treatment febrile reaction.

In view of the promising phase II data, the negative phase III results were disappointing. Although it may have been intuitive to abandon the VB-111 development program for GBM at this stage, we believed that a closer look into the data and careful inspection of all differences between the two studies is warranted before deciding on next steps. It was clear that the distributions of baseline prognostic factors between the two studies were comparable and could not explain the different survival outcomes. However, there was a major difference in the treatment regimen used in each of the studies while the phase II treatment regimen included VB-111 monotherapy priming, the GLOBE treatment arm included upfront a combination of VB-111 and bevacizumab, without a priming period.

Thus, it was hypothesized that the contradictory outcomes are related to the lack of VB-111 monotherapy priming. Although VB-111 and bevacizumab are both anti-angiogenic agents, their mechanism of actions differ: bevacizumab antagonizes VEGF, while VB-111 directly disrupts the angiogenic vessels and induces a tumor directed immune response. It is plausible that the concomitant administration of bevacizumab interfered with VB-111’s action. At the cellular level, bevacizumab normalizes angiogenic cells which are the target for VB-111. Therefore, in the absence of angiogenic cells, VB-111 will not be able to trigger an effect, and at the molecular level the VB-111 promoter (PPE-1) is activated by VEGF, and lack of VEGF reduces promoter-regulated transgene expression and prevents VB-111 activity.

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This hypothesis was reinforced by the unfavorable survival outcomes of the small group of patients in the phase II study’s unprimed combination group that received, just as in GLOBE, concomitant VB-111 and bevacizumab. Further support was provided by pre-clinical studies in mice assessing tumor burden in the Lewis Lung Carcinoma model, where co-administration of bevacizumab and VB-111 blocked the anti-tumor effect of VB-111, and by the unique MRI signature seen in the phase II trial after VB-111 priming, which was not repeated in the GLOBE study.

The emerging picture from this analysis points to study regimen as a key factor for VB-111 efficacy in rGBM, and warrants further evaluation of regimens employing priming with VB-111 in GBM patients. Indeed, the Dana-Farber Cancer Institute is sponsoring a randomized, placebo controlled, phase II study of neoadjuvant and adjuvant VB-111 for patients with rGBM who are undergoing a second surgery. Important lessons from GLOBE were applied to the study design and all patients will be primed with VB-111 monotherapy prior to any bevacizumab administration. This will be the first study to assess neoadjuvant administration of VB-111, which may be the most appropriate therapeutic window for immunotherapy treatments in rGBM.

Patients will be randomized before surgery to one of three treatment arms: 1) VB-111 before and after the surgery (neoadjuvant and adjuvant therapy); 2) VB-111 just after the surgery (adjuvant therapy); 3) standard-of-care control arm. The primary endpoint is to investigate whether administration of VB-111 as a neoadjuvant treatment prior to surgery can result in an increase in tumor-infiltrating T lymphocytes within the tumor and enhance systemic tumor-specific T-cell responses. Secondary endpoints will include progression-free survival at 6 months (PFS-6) and OS. The study’s IND has been approved by the FDA, and it will open during 2020 in seven leading neuro-oncology centers in the U.S.: Dana-Farber Cancer Institute, Massachusetts General Hospital, UCLA, UCSF, University of Utah, Memorial Sloan Kettering, and University of Texas.

The path to pharmaceutical advancements for grave conditions is never easy. Nevertheless, the scientific community together with the industry shall continue to search high and low for novel treatment alternatives that will give hope to patients with GBM.

PATRICK WEN, MD, is a Professor of Neurology at the Harvard Medical School and Director of the Center for Neuro-Oncology at the Dana-Farber Cancer Institute in Boston. He served until 2019 as the President of the Society for NeuroOncology (SNO). TIMOTHY F. CLOUGHEESY, MD, is the Director of the UCLA Neuro-Oncology Program and Professor of Neurology at the David Geffen School of Medicine at UCLA.