

Immunotherapy Combinations Offer Hope in Glioblastoma

By Gina Battaglia, PhD

Immunotherapy has shown promise for treatment of glioblastoma multiforme (GBM), the most common primary brain tumor in adults with historically poor prognosis, but experts agree that combination regimens have the greatest potential to achieve durable response. This is because GBM exhibits powerful adaptive capabilities, a relative lack of immunogenicity, an immunosuppressive tumor microenvironment, and intratumoral heterogeneity. “We’re not going to hit a home run with any treatment [on its own],” said David A. Reardon, MD, clinical director, Center for Neuro-Oncology, Dana-Farber Cancer Institute.



Eric C. Holland, MD, PhD

Greater knowledge about the relationship between molecular subtypes and prognosis, the function of the immune system in the tumor microenvironment, and response of the tumor to targeted agents have helped to clarify why chemotherapy, radiation, and targeted therapy have been generally ineffective against GBM, according to Eric C. Holland, MD, PhD, director, Seattle Translational Tumor Research at Fred Hutchinson Cancer Research Center. He stated that although median survival has inched upward, continued research on the biologic behavior of GBM in response to novel treatments will help to refine these therapies and determine the subgroups of patients who will benefit from them.

Because GBM is highly heterogeneous among individuals, careful selection of patients will be important for assessing treatment efficacy in clinical trials, Holland said. “I think things are getting better slowly, but really getting our hands around the biology of this and optimizing everything is

about as good as we’re going to get until [there is a breakthrough],” said Holland.

Current Standard of Care

The current standard-of-care therapy is maximal surgical resection, followed by concomitant radiation therapy plus temozolomide for 6 weeks and then adjuvant temozolomide for 6 monthly cycles. This treatment strategy gained traction from a phase III trial, published in 2005, that reported median overall survival (OS) of 14.6 months.¹ Results from a clinical trial showed that the addition of a tumor-treating fields device (Optune) to adjuvant temozolomide significantly improved median OS over temozolomide alone (20.5 vs 15.6 months; $P = .004$)² and led to approval of an expanded indication by the FDA for newly diagnosed GBM in 2015.³

However, recurrence is virtually guaranteed with GBM, and none of the currently approved options have demonstrated an OS benefit, although bevacizumab (Avastin) was approved based on improved progression-free survival (PFS) and response rate,⁴ and the Optune device was approved based on the improved response rate and quality-of-life scores.⁵ “Our standard of care leaves a lot of room for improvement,” Reardon said.

Immunotherapy

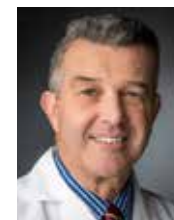
Experts agree that therapies targeting the immune system will likely play a central role in improving durability of treatment. “It’s hard to imagine that anything we do that is successful isn’t going to have some sort of immunotherapy component,” said Holland. However, most agree that a combination approach will probably be necessary given early data showing modest survival benefits of

single-agent immunotherapies. “What we’re really going to need to do is to bring them together in rationally designed combinations, based on as much preclinical work [as] we can gather, to help guide us toward developing in clinic,” said Reardon.

CAR T-Cell Therapies

Chimeric antigen receptor (CAR) T-cell therapy involves modification of a patient’s extracted T cells to express tumor-specific receptors on the surface, followed by reinfusion of the T cells, which can then recognize and kill the tumor cells, into the patient. Some CAR-T cell therapies have demonstrated clinical activity, and a case report demonstrated a 7.5-month continued clinical response after administration of CAR T-cell therapy against interleukin-13 receptor alpha 2, a glioma-associated antigen, in a patient with recurrent multifocal GBM.⁶

However, Reardon stated that the intratumoral heterogeneity presents a major challenge for obtaining long-term clinical benefit from immunotherapies targeting a single antigen. Results from a study showed movement of peripherally infused epidermal growth factor receptor variant III (EGFRvIII)-directed CAR T cells to GBM sites and decreases in the EGFRvIII antigen in the surgical specimens of patients with recurrent GBM.⁷ However, further in situ evaluation revealed increased expression of inhibitory molecules and infiltration by regulatory T cells after infusion, suggesting that durable treatment that includes EGFRvIII-directed CAR T cells will likely require additional interventions to



David A. Reardon, MD

overcome these adaptive changes and address antigen heterogeneity.

Reardon also noted that an EGFRvIII-positive tumor may express the oncogene on only 5% of the tumor cells and that the heterogeneity of EGFRvIII expression may facilitate the emergence of an EGFRvIII-free subclone of the tumor. He also pointed out that approximately 30% of tumors that are initially EGFRvIII-positive lose expression of this oncogene upon recurrence and that this may contribute to the lack of long-term efficacy with therapies targeting EGFR, evidenced by the failure of rindopepimut (Rintega), a peptide vaccine targeting EGFRvIII, to improve OS in the phase III ACT IV study.⁸

“Cells that downregulate or are able to lose expression of EGFRvIII but maintain growth and proliferative capability—that percentage of the tumor is able to take over and become the dominant population of the tumor,” said Reardon. “The ability to lose the expression and become the predominant component of the tumor drives resistance.” He concluded that while targeted therapy may benefit a small subset of patients, additional therapies will likely be needed for any targeted treatment to benefit a broader group of patients.

Virus-Based Therapies

Oncolytic virus therapy, which involves intratumoral injection of a virus genetically engineered to selectively replicate and kill cancer cells, has also shown promise in preclinical and early-stage clinical trials. More than 20 oncolytic viruses are in clinical development for glioblastoma, according to Reardon, with the adenovirus-based DNX-2401 (tasadenoturev) furthest along in the clinical trial stages. Data from a phase Ib trial⁹ showed that a single intratumoral injection of DNX-2401 led to OS rates of 33% and 22% at 12 and 18 months, respectively, in patients with recurrent glioblastoma. The addition of interferon gamma was poorly tolerated and did not provide additional benefit in an intention-to-treat analysis, but the CAPTIVE trial (NCT02798406) is currently investigating the efficacy of intratumoral injection DNX-2401 followed by intravenous pembrolizumab at 3-week intervals for patients with recurrent GBM.

Another approach combines vocimagene amiretrorepvec (Toca 511), an injectable retroviral replicating vector that encodes the gene for cytosine deaminase, with orally administered extended-release 5-fluorocytosine (Toca FC), which is converted to the anticancer agent 5-fluorouracil in cancer cells containing cytosine deaminase. Early data from a subset of 24 patients that mirrored the phase II/III study population demonstrated an overall response rate (ORR) of 21% that was maintained for a median of 26.7 months.¹⁰

In addition to the intratumoral response, these virus-based therapies also activate a systemic immune response to the virus and the tumor, which likely contributes to the long-term benefits observed in responders, according to Linda M. Liau, MD, PhD, MBA, neurosurgeon and director of the UCLA Brain Tumor Program.

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—Eric C. Holland, MD, PhD

“Injecting the virus into the tumor creates an immune environment as the tumor dies off that enhances the immune response in the tumor,” Liau said.

Dendritic Cell Vaccines

Dendritic cell vaccines, which involve harvesting the patient’s dendritic cells, exposing them to tumor-specific peptides or tumor lysates, and injecting them back into the patient, demonstrated improvements in overall and 2-year survival over conventional therapy in a systematic review of 6 comparative clinical trials.¹¹

According to Liau, the response to dendritic vaccine therapy may vary among GBM subtypes. She noted that in a phase IIa trial¹² of an autologous tumor lysate-pulsed dendritic cell vaccine for patients with grade 2 gliomas, long-term survivors tended to have a mesenchymal subtype. Although this association has yet to be confirmed in phase III trials, she suggested that the mesenchymal subtype is more immunogenic, as the tumor had more T cells prior to treatment, and likely has a different pathogenesis from that of other subtypes, such as the relatively nonimmunogenic proneural subtype.

Checkpoint Inhibitors

Checkpoint inhibitors have had minimal success

when added to current standard-of-care therapies in recent clinical trials. KEYNOTE-028,¹³ a phase I trial that investigated the PD-1 inhibitor pembrolizumab in solid tumors and included a cohort of 26 patients with glioblastoma, showed that 13 patients exhibited a partial response or stable disease, but this did not translate into significant improvements in PFS or OS. According to Liau, the relative lack of immunogenicity in newly diagnosed GBM is a key factor contributing to the minimal activity of immune checkpoint inhibitors. “At baseline, they don’t attract many T cells, so there’s no point in unblocking the immunologic block if there’s no traffic going through anyway,” said Liau.

However, she noted that immunotherapeutic approaches such as dendritic cell vaccines and oncolytic viruses may induce a host immune response at the tumor site, providing an environment in which checkpoint inhibitors exert clinical activity. She and her colleagues recently published a preclinical study¹⁴ of human tissue samples and a murine model that identified a population of tumor-infiltrating myeloid cells that increased with dendritic cell vaccine therapy and accounted for the majority of PD-L1 expression in the tumor microenvironment. Furthermore, treatment with a PD-1 inhibitor and colony stimulating factor 1 receptor inhibitor significantly improved survival in the mouse model, suggesting that the addition of a checkpoint inhibitor or another agent that blocks the tumor-infiltrating myeloid cells may help patients who demonstrate a less durable response to vaccine therapy.

“There are probably going to be subgroups of patients who have different responses to immune or vaccine therapy,” said Liau. “Going into the future, we need to figure out who will respond to which type of therapy.”

Antibody-Drug Conjugates

EGFRvIII, a tumor-specific, constitutively active form of EGFR, is found in 20% to 30% of glioblastomas. However, monoclonal antibodies (eg, rituximab [Rituxan]) and small molecules targeting EGFR such as erlotinib (Tarceva) and gefitinib (Iressa) have not shown efficacy in GBM, in part because commonly used EGFR-targeted therapies do not work with the EGFR abnormalities, amplifications, or mutations in the extracellular domain in GBM, said Martin J. van den Bent, MD, PhD, of the Erasmus MC Cancer Center in Rotterdam, the Netherlands, in an interview with *OncLive*.¹⁵

ABT-414 is composed of a tumor-specific anti-EGFR antibody (ABT-806) linked to monomethyl auristatin F, a microtubule cytotoxin, and



Martin J. van den Bent, MD, PhD

selectively targets cells with EGFR amplification, overexpression, or mutation (such as EGFRvIII). According to van den Bent, ABT-414 acts like a “Trojan horse” because the tumor’s EGFR receptor is targeted to internalize the compound and increase the cytotoxic effect in the tumor cell. A pooled analysis of 126 patients with EGFR-amplified recurrent GBM demonstrated an ORR of 10.4% and disease control rate of 52%.¹⁵

The follow-up phase IIb/III Intellance1 trial (NCT02573324) will randomize patients with newly diagnosed GBM to receive ABT-414 or placebo along with standard-of-care therapy. Positive outcomes in this trial could indicate an additional therapy to add to the standard of care for patients with EGFR-amplified GBM, as well as a proof of principle for more effective delivery of other targeted agents, van den Bent said.

According to Holland, the increase in concentration of cytotoxic agents within the tumor cells with this “Trojan horse” mechanism may also kill cells adjacent to the target, even if they do not express the EGFR mutation. However, he cautioned that the heterogeneity of the cells within GBM tumors makes it difficult to predict the success of therapies relying on a single target. “We’re looking for the therapeutic window, but the problem is that the population you’re targeting is very heterogeneous and they’re not all going to have the thing you want to target,” said Holland. “That’s been the general problem all along, from small molecules to antibodies to radiation.”

Clinical Trial Design: Key to Optimizing Treatment

Until recently, the World Health Organization (WHO) classification of primary brain tumors has been based solely on histopathologic criteria. However, large-scale efforts such as The Cancer Genome Atlas (TCGA) Network demonstrating the clinical relevance of genetic and epigenetic alterations prompted the creation of diagnostic entities that integrate histopathology and molecular signatures in the 2016 WHO classification system.¹⁶

According to Holland, genetics are a major driver of tumor behavior and response to treatment and should be considered when assessing efficacy of a given treatment in clinical trials and predicting which patients will respond. “If your control arm happens to have a lot of patients who are genetically different from your study arm, you could make a drug that actually works quite well look no good at all,” he said.

A recent example of the control arm performing better than expected was the recently discontinued phase III ACT IV trial,⁸ in which the median OS was 21.1 months in the control group and 20.4 months in the experimental group receiving

rindopepimut. Although the investigators are still researching why the control arm performed better than they expected with standard-of-care therapy (approximately 15 months), Holland stated that genetic analyses of tumors should be incorporated more broadly in the design of trials for GBM. “We have that technology now...That’s the kind of thing that, when we design trials, we should watch carefully to make sure we’re not running off the rails. Failure to do so might be contributing to some of our troubles as far as outcomes.”

Holland also emphasized that post hoc genetic characterization of responders can help optimize trial design throughout the clinical trial process to home in on subgroups of patients who should be studied in future trials. “You have some responders; it could be that they’re all responding from a particular type of genetics that you should in fact be running your next trial on and not diluting it with patients who aren’t going to respond,” he said.



Linda M. Liao, MD, PhD, MBA

Liao also stated that characterizing the changes in tumors from initial diagnosis to the recurrent setting through gene sequencing or biomarker analysis may help predict which treatment approaches will be most effective over time for different subtypes of GBM. “Even if you’re able to reduce the tumor growth because you targeted the mutation, the tumor comes back later with a different set of mutations,” said Liao. “We’re finding that when we do our recurrent tumor sections, the tumor after treatment is not the same as the tumor [was] before [treatment].”

Overall, experts agree that effective treatment approaches will likely vary among individuals, as GBM is not “one size fits all” in terms of treatment. “Each patient’s tumor is unique, and the closer we can get to being able to individualize and utilize treatments specifically, the better chance we have of helping that individual,” said Reardon. ■

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