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Immunotherapy for High-Grade Gliomas: A Clinical Update and Practical Considerations for Neurosurgeons

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Abstract

BACKGROUND: The current standard of care for patients with high-grade gliomas includes surgical resection, chemotherapy, and radiation; but even still most patients experience disease progression and succumb to their illness within a few years of diagnosis. Immunotherapy, which stimulates an anti-tumor immune response, has been revolutionary in the treatment of some hematologic and solid malignancies, generating substantial excitement for its potential for patients with glioblastoma. However, to date, the preclinical success of these approaches against high-grade glioma models has not been replicated in human clinical trials. Moreover, the complex response to these biologically active treatments can complicate management decisions, and the neurosurgical oncology community needs to be actively involved in and up to date on the use of these agents in patients with high-grade glioma. In this review, we discuss the challenges immunotherapy faces for high-grade gliomas, the completed and ongoing clinical trials for the major immunotherapies, and the nuances in management for patients being actively treated with one of these agents.

METHODS: We reviewed the literature to summarize the current immunotherapy strategies for high-grade gliomas.

RESULTS: Preclinical and clinical trials investigating dendritic cell and peptide vaccines, checkpoint inhibitors, and adoptive T cell therapy are high-lighted in this review.

CONCLUSIONS: Although immunotherapy has yet to fully fulfill its promise for patients with glioblastoma and improve patient outcomes, there is still excitement that these approaches will eventually lead to durable anti-tumor responses. As neurosurgeons, an understanding of the complex interactions between the standard of care therapies and the other medications used in the treatment arsenal for patients with high-grade brain tumors is crucial to the management of these patients.

Keywords

Adoptive T cell therapy; Cerebral edema; Checkpoint inhibitors; Corticosteroids; Dendritic cell vaccines; Peptide vaccines

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INTRODUCTION

Initially described as an immunologically inert organ because of the blood-brain barrier (BBB) and lack of lymphatic drainage, the central nervous system is now known to be actively surveilled by the immune system.[1] However, in patients with glioblastoma (GBM), there are both local and systemic immunosuppressive obstacles impairing any possible antitumor response.[2,3]

Melanoma and non-small-cell lung cancer are the 2 solid tumors in which immunotherapy has shown the most success. In 2010, ipilimumab (a cytotoxic T-lymphocyte–associated protein 4 [CTLA-4] blocking monoclonal antibody) was approved by the U.S. Food and Drug Administration for treatment of metastatic melanoma.[4] Nivolumab and pemrolizumab, programmed cell death protein (PD)-1 monoclonal antibodies, are other checkpoint inhibitors that have received Food and Drug Administration approval.[5] Although one recognizes these successes, one must acknowledge that these 2 tumors are among the most mutagenic solid malignancies, which in theory increases the number of neoantigens available for presentation to the immune system.[6] Thus, these successes may not be applicable to GBM, which is in the middle of the spectrum for degree of mutagenicity.

There are many unique challenges that immunotherapy must overcome to be successful in the brain. First, anatomically, the BBB restricts the entry of immune cells to the brain parenchyma.[7] Also, the tumor cells themselves secrete a variety of immunosuppressive factors that influence macrophage polarization, dendritic cell (DC) maturation, regulatory T cell recruitment, and inhibition of neutrophil and natural killer cell function.[8] In addition, glioma cells express on their surface molecules such as PD-L1 and CD95 that inactivate and have an apoptotic effect on infiltrating T cells. Moreover, immunosuppressive cells such as Tregs, M2 phenotype macrophages, and myeloid derived suppressor cells which dampen any potential antitumor immune response.[9] Nevertheless, there are preclinical data showing the successes of immunotherapy for gliomas, which have led to numerous clinical trials investigating its potential benefit in human patients.[10]

In this review, we summarize the literature for peptide and DC vaccines, checkpoint inhibitors, and adoptive T cell therapies for patients with high-grade gliomas and highlight importance practical considerations for neurosurgeons managing this patient population. We focus on the challenges and shortcomings of immunotherapy (see Table 1 for a list of completed clinical trials) and point out specific areas in which neurosurgeons can influence the field during the intraoperative and perioperative management of patients receiving these agents.

PEPTIDE AND DC VACCINE THERAPY

Peptide Vaccines

Peptide vaccines are designed to illicit an immune response by activating native DCs and can be directed against a single antigenic target, a predetermined panel of tumor antigens, or patient-specific antigen cluster acquired from tumor lysate.

Targeting EGFRvIII, a mutant form of EGFR that is expressed in GBM, is a prime example of a single antigen-base peptide vaccine and has been extensively studied in the clinical setting. Three phase 2 clinical trials all showed improved progression-free survival (PFS) and overall survival (OS) when using rindopepimut (also known as CDX-110). After these initial successes, the ACT-IV or Phase III Study of Rindopepimut/GM-CSF with Newly Diagnosed Glioblastoma trial was a phase 3 placebo-controlled trial of rindopepimut in patients with newly diagnosed GBM who specifically harbored the EGFRvIII mutation. An interim analysis resulted in termination of the study because of futility. Even although a strong humoral immune response to the vaccine was generated, this did not translate to survival benefits. Importantly, EGFRvIII expression was lost in about half of patients in each arm of the study, showing that EGFRvIII expression is unstable and immune escape may occur.[11] In addition, only up to 30% of patients with high-grade gliomas harbor the EGFRvIII mutation, indicating its limited applicability for this patient population.[33] The ReACT trial was another randomized placebo-controlled trial investigating the effect of rindopepimut in patients with recurrent GBM. Although OS seemed to be improved (11.3 vs. 9.3 months), the primary end point of improved PFS was not met.[34] Even if these trials were successful, only approximately 30% of patients with GBM have EGFRvIII-expressing tumors and would benefit from the therapy.

Izumoto et al.[35] reported outcomes in 21 patients with WT1/HLA-A*2402-positive recurrent GBM who received intradermal injections of a modified WT1 peptide for 12 weeks (preclinical experiments showed the potential for targeting WT1, Wilms tumor gene, with immunotherapy). Median PFS was reported to be 20.0 weeks, [36] and a follow-up study found that the production of WT1 IgG antibody was positively correlated with both PFS and OS.[37] Another target under investigation is IDH1R132H, which is expressed in most low-grade astrocytomas and oligoden-drogliomas and is intracellular and likely a CD4 epitope.[38] PEPIDH1M vaccine is an IDH1-R132H-specific vaccine that contains peptides that span the length of mutated IDH1-R132H and is administered with granulocyte-macrophage colony-stimulating factor (GM-CSF) mixed with Montanide ISA 51, which is an immune modulator. This vaccine is administered intradermally, and it has shown induction of immune response in vitro and in vivo.[39] However, the exact mechanism of action for targeting the mutant intracellular IDH1-R132H is not well understood, and the intracellular nature of the protein may be a limitation of this target.

Given the limitations of single antigen peptide vaccines such as eliciting immune response against only a subset of tumor cells and developing resistance to therapy as a result of shedding the targeted antigen, multipeptide vaccines are attractive because they may offer more prolonged control of tumor growth.[40-42] A 3-peptide vaccine derived from glioma-associated antigens has been used in children with newly diagnosed gliomas and this vaccine was well tolerated and generated measurable immune responses.[19,43] In addition, IMA950, a vaccine including 11 tumor-associated peptides and a synthetic hepatitis B virus marker peptide, was explored in a phase 1 trial with 45 patients undergoing tumor resection. IMA950 was injected intradermally either before or just after initiation of chemoradiotherapy. Most patients were found to be responders. PFS was 74% at 6 months, and median OS was 15.3 months.[15]

Crane et al.[44] examined safety and OS in 12 patients with recurrent GBM receiving a heat shock protein peptide complex (HSPPC-96), which consists of the HSP gp-96 connected to antigenic peptides. An HSP-96-specific immune response was seen in all but 1 patient. These immune responders had a median survival of 47 weeks after surgery/vaccination compared with 16 weeks for the patient who showed no immune response. In a separate phase 2 single-arm study, Bloch et al.[22] reported on 41 patients with recurrent GBM who underwent gross total resection and received multiple doses of the HSPCC-96 vaccine. PFS and OS were found to be 19.1 and 42.6 weeks, respectively. Patients who had a lymphocyte count lower than the cohort median showed decreased OS. The results from the interim analysis of the randomized phase 2 trial investigating HSPPC-96 with bevacizumab for surgically resectable recurrent GBM failed to show any survival benefit compared with bevacizumab alone.[45]

DC Vaccines

Rather than administering peptides directly, autologous DCs (professional antigen-presenting cells) can be loaded ex vivo with either a single tumor antigen or multiple antigens via a tumor lysate and then administered back to patients. Typically, at the time of surgical resection, a tumor lysate is created.[46] The patient also undergoes leukapheresis to harvest DCs. The DCs are then pulsed with either messenger RNA or tumor antigens and then primed to stimulate them to express major histocompatibility complex (MHC) molecules showing tumor antigens before being reintroduced to the patient as a vaccine.

One strategy is for DCs to be exposed to a single GBM-specific antigen. Sakai et al. administered WT1-pulsed autologous DCs in 7 patients with high-grade glioma. Although some patients received tumor lysate pulsed DCs as well, OS starting from the first DC vaccination was 12.3 months for the cohort.[47] Cytomegalovirus-related peptides (e.g., pp65) have also been incorporated into DC vaccines because these viral particles have been found to be specifically present on most GBM cells. Mitchell et al.[48] reported promising PFS (15.4–47.3 months) and OS (20.6–47.3 months) results after delivering pp65-specific DCs combined with vaccine site preconditioning using tetanus-diphtheria toxoid. Batich et al. reported on safety and feasibility in a phase 1 vaccine trial with pp65-DCs mixed with GM-CSF after dose-intensified temozolomide (TMZ). TMZ was used both for its antitumor effect and to bolster de novo expansion of vaccine-induced antigen-specific immune responses in the setting of leukopenia (see later discussion). Median PFS and OS were reported to be 25.3 and 41.4 months, respectively, exceeding survival using recursive partitioning analysis and matched historical controls.[13]

Other DC-based vaccine trials have exposed DCs to multiple tumor antigens to provide several possible targets for the immune system. Phuphanich et al.[49] reported the safety of an autologous DC vaccine pulsed with 6 proteins abundant within the cancer stem cell population of GBM (gp100, MAGE1, AIM2, HER2, IL-13Rα2, TRP2) in a phase 1 clinical study (ICT-107). Immune response data showed that 33% of patients were responders and a decrease in CD133 expression (marker for cancer stem cells) in 5 patients who underwent repeat resection. Although a phase 2 trial involving ICT-107 did not meet the primary end point of improving survival, post hoc analyses showed a possible benefit

within the subgroup of HLA-A2-positive individuals.[50] A phase 3 trial is under way with its enrollment limited to HLA-A2-positive patients. In another phase 1/2 DC-based multipeptide vaccine trial, Okada et al. administered α-type I polarized DCs loaded with EphA2, IL13Rα2, YKL-40, and gp100 at 2-week intervals intranodally in conjunction with biweekly intramuscular injections of poly-ICLC. The investigators reported that >50% of patients had a positive immune response against ≥1 of the vaccination-targeted glioma-associated antigens, and 40% of patients had ≥12 months of PFS, with 22% of patients showing no progression at the time of publication.[51]

Other groups have exposed DCs to tumor lysate, allowing for patient-specific vaccine therapies (e.g., DCVax). Although this approach may allow for more tumor-related antigens to be targeted, there is also a theoretically higher risk of an autoimmune response, although autoimmunity has not been observed in studies using this approach. Chang et al.[52] reported on outcomes from a DC vaccine after coculture of DCs with a patient's own tumor cells. This patient-specific approach was associated with a median survival of 1.4 years. In a phase 1 trial[53] assessing the safety and feasibility of autologous DCs that had been pulsed ex vivo with autologous tumor peptides, increased intratumoral infiltration by cytotoxic T cells was detected in half of the patients who underwent reoperation. This vaccine was later combined with toll-like receptor agonist treatment and there was a median OS of 31.4 months.[54]

One intraoperative consideration for the surgeon is which tissue is ideal to sample or resect for the generation of tumor lysate DC vaccines and how much tissue is needed. Samples can conceivably come from numerous areas within the tumor: the contrast enhancing portion, the necrotic center, the most metabolically active area. Although more work is needed to better understand how the tumor genotype and microenvironment differ in these different areas, it may be beneficial to sample from multiple distinct areas and discuss potential sites with our neuroradiology colleagues to ensure that the sample collected appropriately captures the diverse mutations and invasive subset of cells found within the tumor.

Checkpoint Inhibitors–PD-1/PD-L1 and CTLA-4

Maintaining immune homeostasis and preventing uncontrolled immune responses to pathogens is critical to avoid inflammatory tissue damage and autoimmune disease. To achieve this goal, immune responses are regulated by a balance between stimulatory and inhibitory signals. These inhibitory signals are collectively referred to as immune checkpoints.

The most extensively studied inhibitory checkpoints on T cells are CTLA-4 and PD-1/PD-L1. These surface proteins are upregulated in GBM and hinder T cell activation. In addition, these molecules also have prognostic importance for patients. PD-L1 has been shown to be expressed in some patients with GBM, and its expression is upregulated compared with low-grade gliomas.[55] Moreover, PD-L1 expression on tumor-associated macrophages has been associated with worse prognosis in patients with GBM.[56] The goal of checkpoint inhibitors is to block the inhibition signal and allow for immune stimulation to generate an antitumor response. These checkpoint inhibitors were initially trialed in patients with melanoma and ipilimumab, an anti-CTLA-4 monoclonal antibody, and nivolumab, an anti-PD-1 monoclonal antibody, proven to improve survival in patients with metastatic

melanoma.[4,57] Although preclinical data have been promising for the use of checkpoint inhibitors in patients with glioma,[58-60] the results of the completed clinical trials have not yielded the same promising results.[61]

Checkmate 143,[25] a randomized phase 3 clinical trial evaluating nivolumab (anti-PD-1 monoclonal antibody) compared with bevacizumab in patients with recurrent GBM, did not show a survival benefit. Despite the failure of this trial, there remains a strong interest in checkpoint inhibition for the treatment of GBM and future work is attempting to identify reasons for treatment failure, augment tumor response to nivolumab, and identify patients most likely to benefit from checkpoint inhibition.[62] In nonrandomized exploratory analyses from this trial, there is some signal that combination of nivolumab with ipilimumab (anti-CTLA-4 monoclonal antibody) leads to a durable antitumoral response in a subset of patients, but this combinatorial approach does increase the risk of having a grade 3 or 4 serious adverse event.[63]

Other ongoing clinical trials are evaluating the safety and efficacy of adjuvant checkpoint inhibition in combination with standard-of-care treatment. For example, CheckMate 548 is a phase 3 randomized trial studying nivolumab with radiation therapy and TMZ compared with patients who receive standard-of-care radiation and TMZ in newly diagnosed O6- methylguanine-DNA methyltransferase (MGMT)-methylated patients with GBM. CheckMate 498 is a similar phase 3 trial for patients with MGMT-unmethylated tumors. In addition, 2 checkpoint inhibitor agents in combination are also under investigation given the possibility for synergistic effects. For instance, GlitlpNi is a phase 1 trial (NCT03233152) using intratumoral ipilimumab and systemic nivolumab.

Most clinical trials use systemic administration of antibodies targeting PD-1, which may limit the delivery of the drugs to the tumor site because of the BBB.[64] Although there is an increased permeability of the BBB in patients with GBM and these molecules also likely work on the peripheral circulating lymphocytes,[65,66] the importance of the route of administration has yet to be fully elucidated.

ADOPTIVE T CELL THERAPY

Adoptive T cell therapy is therapy in which engineered or targeted tumor-specific T cells are administered, migrate to tumor cells, detect tumor-specific antigens, and initiate tumor cell death. Because T cells are the main effector cell of the adaptive immune system, this class of immunotherapy has main theoretical advantages: T cell responses were robust and specific, could distinguish between tumor and healthy tissue, and could hone in on malignant cells to target distant metastases. Moreover, T cells can proliferate to sustain and maintain their therapeutic effect.

Adoptive T cells have shown benefit in refractory B-cell cancers and are being applied to many solid malignancies.[67-69] Preclinical models using this therapeutic approach have targeted IL13Rα2, EphA2, EGFRvIII, HER2, and viral particles that are expressed on the surface of tumor cells, with some antigen targets progressing to human clinical trial use.[70]

Brown et al. reported on the first-inhuman evaluation of safety and feasibility of administering autologous chimeric antigen receptor (CAR) CD8+ T cells in patients with recurrent GBM. In the initial report of 3 patients, T cells were designed to target IL13Rα2 and were administered directly into a glioma resection cavity through a catheter. Antiglioma responses were observed in 2 patients, including an increased necrotic volume on magnetic resonance imaging (MRI), significant loss of the IL13Rα2 tumor cell expression, and detection of transferred T cells within tumor microfoci at the site of injection. One drawback with the therapy was that the manufacturing time frame was cumbersome and required 3–4 months to generate the final therapeutic product for each patient.[30] A follow-up report showed a remarkable response in a patient with multifocal GBM with leptomeningeal involvement. In this particular patient, CAR T cells targeting IL13Rα2 with incorporated CD137 costimulation (this costimulation molecule is critical for the ongoing proliferation of these administered cells) and a mutated IgG4-Fc linker to reduce off-target interaction were initially administered into the resection cavity, with observed stable disease at this site. However, over time, new lesions and progression of nontreated distant lesions (including spinal lesions) were observed so additional T cells were administered via an intraventricular catheter. Regression of all intracranial and spinal tumors was observed, which is even more remarkable given the nonuniform tumor expression of IL13Rα2. Consistent with previous reports, CAR T cell accumulation and expansion in the cerebrospinal fluid were limited.[31,71,72]

In addition to HER2, EGFRvIII, and IL13Rα2, autologous T cell therapy has also been designed to target viral particles found on GBM cells and not on surrounding neural and glial tissue. Schuessler et al.[31] reported on the safety and feasibility of administering cytomegalovirus-specific autologous T cells in patients with recurrent GBM and median survival was >1 year.

CAR T cells are limited in part by their inability to target intracellular proteins, the possibility that the tumor may shed the target and escape the therapy, and the lack of persistence and proliferation of the delivered cells. Additional modifications can be made to the T cells to improve their efficacy. For instance, some investigators have engineered the cells so that they can target both tumor-specific antigens as well as viral antigens. With this unique approach, these cells can then receive constant costimulation after any engagement with latent viral antigens, which allows for possible restimulation of the tumor-specific T cells with the subsequent delivery of the viral antigen epitope.[73] Another approach to enhance the effect of CAR T cells is to arm the T cell with the gene for interleukin 12, a potent proinflammatory cytokine that enhances the proliferation and the cytotoxicity of the administered CAR T cells.[74]

ADJUVANT THERAPIES

As described in the introduction, the innate immunosuppression found in high-grade gliomas creates a monumental challenge for immunotherapy that must be overcome to generate a robust immune response against the tumor. One strategy for enhancing the efficacy of these agents is to augment them with adjuvant therapies that tip the overall balance within the tumor in favor of inflammation, antigen presentation, and cell death. Supplementation with

cytokines that shift the microenvironment milieu away from an immunosuppressive state and upregulation of the molecules that express tumor antigens to professional antigen-presenting cells and T cells are 2 approaches that are expanded on in this section.

Chemokines/Cytokines

Chemokines are crucial for the trafficking of immune cells to draining lymph nodes and recruiting antigen-presenting cells and lymphocytes to tumors.[75] Given this role, there has been a focus on their role as a possible synergistic adjuvant to immunotherapy. One such study used CCL3, which recruits multiple types of immune cells, to enhance the recruitment of DCs into the peripheral blood before harvesting the cells for later antitumor vaccination.[76] In addition, one study showed that resistance to checkpoint inhibitors can be overcome in an experimental model of melanoma with the addition of tumor necrosis factor α blockade, which has already been shown to improve some of the immune-related adverse events that are associated with checkpoint inhibition.[77] Exploration of various chemokines and cytokines could result in a favorable shift of the inflammatory milieu to a state in which antitumor immune activation can be robustly achieved.

MHC Upregulation and p53 Mutations

High-grade gliomas are known to down-regulate MHC molecules, which minimizes the amount of antigens that the tumor cells present to the immune system and is associated with shorter survival.[78,79] Exposure to interferon γ has been shown to upregulate MHC class I expression in glioma cells, which may enhance the effectiveness of the immunotherapeutic agent.[80] Radiation has also been shown to increase MHC expression on cancer cells.[81]

Another interesting molecule that may play a potential adjuvant role with immunotherapy is p53. P53, classically described as a tumor suppressor gene that controls cell fate in the setting of DNA damage, also has noncanonical actions on the immune system. Specifically, the activation of p53 leads to a proinflammatory antitumor state.[82] Therefore, strategies that either activate or reintroduce p53, such as viral vectors or targeted small molecules, can be tried with immunotherapy to boost their efficacy. Although these possible synergistic benefits remain theoretical, their potential is an exciting possibility for the future.

ADVERSE REACTIONS

Generally, activation of the immune system by immunotherapeutics results in autoimmune side effects, leading to offsite healthy tissue damage. Hence, evaluating the safety and understanding the immunotherapy-related adverse events has been an area of focus for immunotherapy trials. Commonly, these immune-related adverse events include rash, colitis, esophagitis, and transaminitis. There is also a theoretical risk of neurologic and ophthalmologic symptoms from nonspecific inflammation in the central nervous system and forms of autoimmune encephalitis. The Common Terminology Criteria for Adverse Events (CTCAE) grading system has been used in immunotherapy trials to evaluate the severity and incidence of autoimmune adverse events (Table 2). Compared with other immunotherapy approaches, immunotherapy-related adverse events for checkpoint inhibitors have been the

most extensively studied. Overall, few grade 3 adverse events have been reported with immunotherapy trials.

In phase 1 trials assessing the safety of HER2- and IL13Rα2-targeting CAR T cells, some patients with GBM experienced neurologic side effects including headaches, shuffling gait, or tongue deviation.[30] In a phase 2 clinical trial investigating ipilimumab for patients with melanoma with brain metastases, the most common grade 3 adverse events involved diarrhea, fatigue, dehydration, hyperglycemia, and transaminitis.[26] Confusion was considered a grade 4 adverse event and reported in 2 patients in the study. With respect to nivolumab, similar adverse events such as fatigue, pruritus, rash, vitiligo, constipation/diarrhea, and asthenia have been reported.[83] There seems to be an increased prevalence and severity of autoimmune side effects when checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 are used in a combinatorial fashion.[84] The most common adverse events associated with checkpoint inhibitors include dermatitis enterocolitis, autoimmune hepatitis, pneumonitis, and endocrinopathies There have been case reports of neurosarcoidosis, myositis, myasthenia gravis, and transverse myelitis as well with immune checkpoint inhibitors. In addition, anti-CTLA-4 agents have been associated with higher rates of grade 3–5 adverse events.[85,86]

For vaccine therapy trials, the reported minor adverse events include injection site reactions and fatigue.[22,44] In a phase 2 trial in which patients with GBM were given rindopepimut combined with GM-CSF, primarily grade 2 or less toxicities were seen in patients.[87] Similarly, DC vaccines targeting tumor-specific antigens have been well tolerated, with mostly mild grade 2 or less reactions being reported.[49] These adverse reactions have not been severe enough to require dose limitation.[43,53]

IMMUNOTHERAPY COMBINED WITH OTHER APPROACHES

Combining Immunotherapy with Non-Immunotherapy Approaches

Given the dynamic nature of immune cell responses and the impact of chemotherapy and radiation treatment on the immune system, a complex relationship likely exists when an immunotherapeutic agent is used with another traditional anticancer treatment. Radiation can increase MHC expression on tumor cells and generate danger signals in proinflammatory cells.[81] Lymphopenia is a well-known side effect of TMZ and radiation therapy,[88] and recovery from this chemotherapy/radiotherapy-induced lymphopenia has been shown to potentiate cancer antigen-specific T cell responses and can improve the efficacy of cancer vaccines.[89,90] In addition, although the optimal duration of maintenance TMZ for standard-of-care therapy is debated,[91] it seems that prolonged TMZ exposure induces hypermutations within MGMT-methylated tumor cells.[92,93] Although this situation may accelerate malignant progression, it could also lead to more targets for immunotherapy,[94] particularly because the mutational load found in tumors has been found to correlate with the susceptibility of tumors to checkpoint therapy and treatment-naive GBM has orders of magnitude fewer mutations than melanoma and small-cell lung cancer.[6,95] However, the lymphopenia from prolonged TMZ effect may dampen T cell expansion and impede T cell immunotherapies,[96] so clinicians must consider the class of immunotherapy that they are using when factoring in the decision to continue to TMZ therapy or not.

There are numerous trials showing the synergistic effects of radiation therapy and immunotherapy.[97] In other solid tumors, radiation has been shown to stimulate the release of chemokines that attract cytotoxic T cells and promote a tumor-specific T cell response.[98,99] Given these findings, it is not surprising that Zeng et al.[6] found that in a mouse model of glioma, radiation plus anti-PD-1 antibody prolonged survival in combination, but neither modality was sufficient independently, and the effect was dependent on CD4+ and CD8+ T cells. More work is needed to determine the optimal timing, dose, and target of radiation therapy when combined with various immunotherapy regimens.

Combining checkpoint inhibitors or vaccine therapies with bevacizumab (Avastin) is one clever strategy that tries to reduce the need for corticosteroid therapy with immunotherapy (e.g., NCT 01814813).[100] Although the efficacy of combining checkpoint inhibitors with antiangiogenic therapy has not been reported to date, small pilot studies have shown that this approach is safe (NCT02337491).[101] The hope is to manage cerebral edema with bevacizumab and spare the patient exposure to steroids, which may decrease the efficacy of the checkpoint inhibitor. There are numerous clinical trials exploring different chemotherapeutics and immunotherapeutics with bevacizumab. Although these approaches are under investigation, complex questions regarding the timing, dose, and order of chemoradiation therapy, antiangiogenic therapy, and immunotherapy remain to be answered.

Combinatorial Immunotherapy Approaches

The most promising response rates to immunotherapy for the treatment of solid malignancies have been with combinatorial approaches. For example, combining CTLA-4 and PD-1 checkpoint blockade led to a greater overall response rate for patients with advanced melanoma than either monotherapy alone.[102] In addition, given the relatively small mutational load found in gliomas and the significant intratumoral immunosuppression, monotherapy with a single checkpoint inhibitor seems unlikely to lead to significant improvement in survival, except potentially in patients who have mismatch repair deficiencies or hypermutated tumors after prolonged alkylating chemotherapy.[103,104]

Another interesting combination is using checkpoint inhibitors with antigen-specific vaccines to boost the endogenous T cell response after vaccine therapy, which is being investigated in the AVERT clinical trial (NCT02529072). This strategy makes intuitive sense because the endogenous T cells must overcome the immunosuppressive glioma microenvironment to exert their antitumor effect, and checkpoint inhibitors should augment their ability to accomplish this feat. However, as described earlier, there seem to be more adverse events related to immune activation when multiple immunotherapies are used simultaneously. Finding a balance between sufficient immune activation to overcome the innate tumor immunosuppression and generate a durable treatment response without causing serious autoimmune side effects will be an ongoing focus of future investigations.

NUANCES FOR NEUROSURGEONS

Patient Selection

The remarkable improvement seen for patients with some advanced cancers such as melanoma and lung cancer that are treated with immunotherapy is undeniable; however, even for these responsive tumors, most patients fail to respond to the therapy.[105] Thus, selecting patients who are most likely to respond to a treatment strategy is critical for choosing which immunotherapy to recommend. Obviously, this is paramount for the success of targeted vaccines such as the EGFRvIII-targeted therapy. Also, performing molecular profiling of the tumor can provide information about targets not seen with immunohistochemical staining, which may offer more targets for peptide-based vaccine therapies. Moreover, intratumoral and peripheral expression of PD-L1 may correlate with response rates to PD-L1 monoclonal antibody blockade.[106] Furthermore, it seems that some multipeptide vaccines may be most efficacious in patients with an HLA-A2 genotype, as established for other malignancies such as multiple myeloma and renal cell carcinoma.[107,108] However, this higher efficacy may also be related to the superior ability of the peptides to bind to the HLA-A2 receptor compared with the HLA-A1 variant. These examples show cases where an off-the-shelf therapy can be applied to patients most likely to benefit from the treatment. Even more advanced are personalized vaccines, but these typically require more time to make, require more tissue to generate, and are more difficult to be approved by regulatory agencies, which limits their wide-spread clinical use. Neurosurgeons are critical for appropriate patient selection and can help neuro-oncologists choose therapies by contributing tissue for pathologic analysis, injecting agents intratumorally, and determining how much tumor volume can be removed for the generation of certain vaccine therapies.

Concern for Cerebral Edema and Balancing Symptomatic Edema Management with Corticosteroid-Induced Immunosuppression

One concern with immunotherapy is the possibility of clinically significant cerebral edema in the setting of severe tumor necrosis after the recognition of the tumor by the immune system. Although this situation has not been observed in the randomized controlled trials, there are case reports of patients who experienced a rapid deterioration after drug administration from malignant cerebral edema.[109] Although dexamethasone usually leads to a clinical improvement, the complex relationship of steroids with the immune system likely influences the beneficial effects of immunotherapy agents. Malignant cerebral edema does not seem to commonly affect patients receiving immunotherapy, but as more combinatorial and tailored treatment regimens are tried, neurosurgeons should be mindful of this rare, yet possibly life-threatening, side effect.

The overall impact of dexamethasone use on the effect of immunotherapy is probably dependent on the type of immunotherapy used and the timing of dexamethasone use. For instance, acute use of dexamethasone after administration of adoptive cell therapies likely has little impact on the effect of the therapy because the action of the T cells against the malignancy occurs over weeks to months, whereas acute use of corticosteroids with

checkpoint inhibitors may lead to a significant dampening of the effect of the checkpoint inhibitor.

Given these immunomodulatory effects of dexamethasone, many trials of checkpoint inhibitors for other solid malignancies have excluded patients receiving dexamethasone, although that is not reasonable for patients with high-grade gliomas. One trial exploring ipilimumab for patients with brain metastases from melanoma[26] found that patients receiving corticosteroids during the trial had a worse outcome, although this may be influenced by the fact that the group needing treatment with corticosteroids for symptom relief likely had a poorer clinical status than did the patients who did not require corticosteroid treatment. One study[110] found that CTLA-4 blockade, but not PD-1 blockade, could partially prevent the immunosuppressive effects of dexamethasone in mice with competent immune systems and gliomas. Somewhat surprisingly, the efficacy of anti-PD-1 therapy was not abrogated by dexamethasone administration for mice bearing intracranial tumors; however, mice bearing peripheral tumors saw no benefit from anti-PD-1 therapy when it was given in conjunction with dexamethasone, suggesting that the site of the tumor may play a role in the effect that steroids play on checkpoint inhibitors.[111] Nevertheless, judicious use of corticosteroid dosing is likely ideal until the relationship between their interaction with immunotherapy can be better established.

Imaging Interpretation: Treatment Response versus Tumor Progression

The ability to accurately monitor a patient's response to immunotherapy is critical for evaluation of the effectiveness of the treatment and for guiding future clinical decisions. Given the inflammation and sometimes delayed effect in response to various immunotherapies, determining true tumor progression from treatment effect or pseudoprogression can be challenging with traditional imaging studies. Generally speaking, increasing contrast enhancement, particularly enhancement at sites distant from the treatment sites, and increasing nonenhancing signal abnormality represent tumor progression.[112] Nonenhancing fluid-attenuated inversion recovery abnormality is more concerning for true tumor progression when it is of intermediate intensity, involves the cortex, shows mass effect, or is associated with restricted diffusion or increased perfusion.

RANO (Radiological Assessment in Neuro Oncology) has created a set of immunotherapy guidelines (iRANO) to help guide the radiographic interpretation for patients being treated with immunotherapy.[113] These guidelines highlight how to interpret radiographic progression, which may not be indicative of a lack of treatment response, and other important considerations such as new radiographic lesions, the timing of possible progression in relationship to the delivery of immunotherapy, the importance of repeat imaging to confirm findings, and when to obtain tissue to diagnose true progression.

Supplementing traditional MRI with positron emission tomography (PET) imaging is one approach to help distinguish between tumor progression and treatment response, in which PET imaging of an enzyme overexpressed in immune cells is used to characterize the degree of inflammatory response.[114] It remains to be seen if PET scans or other imaging studies, such as magnetic resonance spectroscopy will become a component of routine surveillance imaging for assessment of treatment response for patients receiving immunotherapy.[115]

Although advanced MRI techniques such as perfusion imaging and molecular labeling of proteins used in metabolic pathways may differentiate treatment effect from tumor progression, other more invasive options exist and are often necessary to truly delineate between the 2 options.[116,117] For example, repeat operation for tissue collection and pathologic analysis offers a definitive diagnosis for a patient. This factor can be critical for evaluating how a patient has responded to treatments aimed at activating the immune system, because the amount of tumor infiltrating lymphocytes and monocytes can be analyzed.

CONCLUSIONS

Although immunotherapy has yet to fully fulfill its promise for patients with GBM and improve patient outcomes, there is still excitement that these approaches will lead to durable antitumor responses. For neurosurgeons, an understanding of the complex interactions between the standard-of-care therapies and the other medications used in the treatment arsenal for patients with high-grade brain tumor is crucial to the management of these patients. In addition, the surgeon's role in the route of delivery, timing of therapy initiation, interpretation of imaging findings, decision to reoperate, and design of trials is paramount to the continued investigation of these agents.

Abbreviations and Acronyms

BBB	Blood-brain barrier
CAR	Chimeric antigen receptor
CTLA-4	Cytotoxic T-lymphocyte–associated protein 4
DC	Dendritic cell
GBM	Glioblastoma
GM-CSF	Granulocyte-macrophage colony-stimulating factor
MGMT	O6-methylguanine-DNA methyltransferase
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
TMZ	Temozolomide

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Table 1.

Summary of Completed Immunotherapy Clinical Trials Highlighting Strengths and Limitations of Each Trial

Immunotherapy Approach	Phase	Sample Size	Overall Survival (months)	Progression-Free Survival (months)	Strengths	Limitations
Vaccines						
International randomized double-blind controlled study of rindopepimut/GM-CSF with adjuvant TMZ in patients with newly diagnosed, surgically resected, EGFRvIII-positive glioblastoma[11]	3	745	20.1	8	First randomized clinical trial evaluating the efficacy of an EGFRvIII-targeted therapy for newly diagnosed glioblastoma	Uncertainties on the significance of the cutoff of EGFRvIII expression for inclusion Vaccine administration schedule designed such that it started after XRT, rather than as early as possible
Prospective, phase 2 clinical trial to evaluate efficacy and safety of autologous DC vaccination in patients with glioblastoma multiforme after complete surgical resection with fluorescence microscope[12]	2	26	23.4	12.7	Improved inclusion and exclusion criteria to better reflect patient population and more accurate survival data Vaccine schedule designed to deliver vaccine before XRT	Selection bias in favor of patients with small superficial tumors as well as those with extensive tumor resection
Antitumor immunotherapy targeted against CMV in patients with newly diagnosed glioblastoma multiforme during recovery from therapeutic TMZ-induced lymphopenia[13]	1	11	18.5	10.8	Provides additional support for targeting the association between CMV and glioblastoma and its use in immunotherapy	Retrospective study design There was no comparison between the efficacy of dose intensified-TMZ alone vs. dose intensified-TMZ plus pp65-DC
Phase 1 study of safety, tolerability, and immunologic effects of SVN53-67/M57-KLH in patients with survivin-positive malignant gliomas[14]	1	9	86.6	17.6	First-in-human study showed the safety, tolerability, and immunogenicity of SurVaxM in patients with recurrent malignant glioma after failure of standard therapy	Small sample size
Phase 1 trial of IMA950 (a novel multipeptide vaccine) plus GM-CSF in patients with newly diagnosed glioblastoma[15]	1	45	15.3	NR	Investigates the most biologically effective and clinically feasible administration schedule	Enrolled patients were not randomized Trial not prospectively powered to compare the 2 cohorts
Phase 1 study of vaccination with lethally irradiated glioma cells mixed with GM-K562 cells in patients undergoing craniotomy for recurrent tumor[16]	1	11	12.4	NR	First study showing safety and feasibility of combining autologous irradiated glioblastoma cells with GM-K562 cells as vaccination in patients who had undergone craniotomy for recurrent tumor	Attrition of enrolled patients because of disease progression or clinical decline
Phase 1 study on the use of racotumomab antiidiotype antibody in patients with pediatric malignancies that express N-glycolylated gangliosides and are resistant to conventional treatment[17]	1	15	3 months after study entry	NR	First phase 1 study showing that racotumomab is safe and immunogenic in a population of pediatric patients with advanced and refractory pediatric tumors	Limited antitumor activity in heavily pretreated patients with refractory malignancies
Phase II study of CDX-110 with radiation and TMZ in patients with newly diagnosed glioblastoma multiforme[18]	2	65	21.8	5.5	Multicenter phase 2 study of CDX-110 with XRT and TMZ confirming the results of improved survival from previous phase 2 trials of rindopepimut	Selected patients have favorable prognostic factors including gross total resection and completion of chemoradiation without progression, which can affect the outcome Small open-label single-arm study design

Immunotherapy Approach	Phase	Sample Size	Overall Survival (months)	Progression-Free Survival (months)	Strengths	Limitations
Pilot study to evaluate the effects of vaccinations with HLA-A2-restricted glioma antigen-peptides in combination with poly-ICLC for adults with World Health Organization grade II low-grade gliomas[19]	1	23	NR	17	First clinical study of peptide-based vaccination using novel glioma associated antigen-derived epitopes and adjuvant poly-ICLC in high-risk World Health Organization grade 2 low-grade gliomas showing tolerability and efficacy of this approach	Unequal distribution of patients among the 3 cohorts, with cohort 2 only having 1 patient
Phase 1 trial on the feasibility and tolerance of treating recurrent glioblastoma multiforme with DC vaccination and TMZ[20]	1	14	23	NR	First phase 1 trial to explore the feasibility of manufacturing autologous monocyte-derived DC-based vaccines in patients with glioblastoma multiforme in which previous exposure to TMZ was an entry criterion	Attrition of enrolled patients because of insufficient yield of DC vaccines (21%), radionecrosis, and rapid progression Limited conclusions can be drawn regarding efficacy of this combination therapy
Phase 1/2a trial of autologous tumor vaccine and TMZ administration in patients with primary glioblastoma[21]	1/2	24	22.2	8.2	Phase 1/2a trial showing the safety of fractionated radiation therapy, TMZ, and tumor vaccine with favorable survival outcome	Characteristics of the patients included in the study were not typical of patients with glioblastoma in general (younger age, and high extent of resection) Selection bias because of including 5 patients who had positive prognostic factors (IDH1R123-H positive) This study does not prove efficacy for the combination of fractionated radiation therapy, TMZ, and tumor vaccine
Phase 1/2 trial of heat shock protein peptide complex 96 vaccine for patients with recurrent high-grade glioma[22]	1/2	41	9.9	4.5	Establishes safety and comparable efficacy of administering heat shock protein peptide complex 96 vaccine for patients with recurrent high-grade glioma	Open-label study design The inclusion criteria of gross total resection and high functional status limits the applicability of the study to all patients with glioblastoma 20% of enrolled patients had insufficient tumor resected to produce vaccine Although progression-free survival is reported, it is not one of the primary end points of the study because of limitations in assessing this metric
Pilot study to evaluate the effects of vaccinations with HLA-A2- restricted glioma antigen-peptides with poly-ICLC for children with newly diagnosed malignant brain stem gliomas, nonbrainstem high-grade gliomas, recurrent low-grade gliomas, or recurrent high-grade gliomas[23]	1	60	13.3	NA	First clinical evaluation of peptide-based vaccination using novel glioma associated antigen-derived epitopes in an emulsion-based vehicle, administered in conjunction with immunoadjuvant therapy for recurrent childhood low-grade gliomas showing reasonable safety and immunologic efficacy of this approach, as well as preliminary evidence of clinical activity	Open-label study design
Phase 1/2 trial of vaccine therapy with tumor stem cell derived messenger RNA-transfected DCs in patients receiving standard therapy for glioblastoma[24]	1	20	25.3	23.1	First study targeting a characterized population of cancer stem cells in gliomas, which also shows feasibility, safety of an active immunotherapy targeting glioma stem cells	Insufficient glioma stem cells to produce vaccines in the treatment group Evaluation of tumor response such as tumor volume is limited because of small sample size

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Immunotherapy Approach	Phase	Sample Size	Overall Survival (months)	Progression-Free Survival (months)	Strengths	Limitations
Checkpoint inhibitor						
Randomized phase 3 study evaluating the efficacy and safety of nivolumab vs. bevacizumab in patients with recurrent glioblastoma: CheckMate 143[25]	3	369	9.8	1.5	First large randomized clinical trial of programmed cell death protein pathway inhibition in the setting of glioblastoma	Open-label study design
Prospective clinical trial designed to evaluate the efficacy and safety of ipilimumab in patients with melanoma metastatic to the brain[26]	2	72	7 vs. 4	NR	First open-label study that established ipilimumab shows activity in melanoma patients with brain metastases, particularly when they have stable, asymptomatic metastases that do not need corticosteroid treatment	Prospective open-label study design Small sample size, preventing formal analysis
Phase 2 clinical trial looking at the effects of pembrolizumab alone or when combined with bevacizumab in patients with recurrent glioblastoma[27]	2	80	8.8 for combination therapy.	4.1 for combination therapy	First study looking at pembrolizumab in combination with bevacizumab	Open-label study design Patients were randomized, but it is difficult to compare the 2 cohorts directly
Adoptive T cell therapy						
Randomized pilot trial in patients with newly diagnosed glioblastoma implicating polyfunctional T cell responses as a biomarker for effective antitumor immunotherapy[28]	1	22	NR	NR	First study to produce and safely administer CMV pp65-specific T cells with DC vaccination (CMV-ATCT-DC) or saline (CMV-ATCT-saline) to patients with newly diagnosed glioblastoma	Single-institution single-blind study design
Multicenter randomized open-label phase 3 clinical trial to assess the efficacy and safety of 'INNOCELL Immuncell-LC' with TMZ in newly diagnosed glioblastoma in Korea[29]	3	180	22.5	8.1	First prospective multicenter randomized controlled study of cytokine-induced killer cells immunotherapy for newly diagnosed glioblastoma	Open-label study design
Pilot feasibility and safety study of cellular immunotherapy for recurrent/refractory malignant glioma using genetically modified autologous CD8+ T cell clones[30]	1	3	11 after relapse	NR	First-in-human pilot safety and feasibility trial evaluating chimeric antigen receptor–engineered, autologous primary human CD8+ cytotoxic T lymphocytes targeting IL13Rα2 for the treatment of recurrent glioblastoma	Small patient population
Phase 1 trial to assess safety of autologous human CMV-specific T cell therapy for glioblastoma multiforme[31]	1	19	13.3	8.2	First clinical trial for adoptive immunotherapy using CMV-specific T cells in patients with recurrent GBM	Attrition from the initial study participants. The number of patients receiving the therapy was 11 No definitive conclusions can be drawn regarding survival
Administration of HER2 chimeric antigen receptor expressing CMV-specific cytotoxic T cells in patients with glioblastoma multiforme[32]	1	16	24.5	3.5 after T cell infusion	First phase 1 dose-escalation study, establishing the safety of autologous HER2-CAR VSTs in 17 patients with progressive glioblastoma	No definitive conclusions can be drawn regarding survival The small sample size, which had attrition from screening patients for HER2 positivity to T cell infusion Study population involved pediatric patients. Inclusion of children (<18 years old), who have a better

Immunotherapy Approach	Phase	Sample Size	Overall Survival (months)	Progression-Free Survival (months)	Strengths	Limitations
						prognosis than adults, might have also affected the outcome

GM-CSF, granulocyte-macrophage colony-stimulating factor; TMZ, temozolomide; XRT, radiation therapy; DC, dendritic cell; CMV, cytomegalovirus; NR, not reported.

Table 2.

The CTCAE Grading System Used to Evaluate Immunotherapy-Related Adverse Events in Immunotherapy Clinical Trials and the General Approach to Management

Grade	Severity	Management
1	Mild: asymptomatic or mild symptoms	Observation only. No interventions required
2	Moderate	Minimal, local, or noninvasive interventions indicated including possible low-dose steroids. Immunotherapy may be continued
3	Severe or medically significant	Severe symptoms require intervention, but not immediately life threatening. Interventions involve stopping immunotherapy and starting high-dose corticosteroids
4	Life-threatening	Urgent interventions indicated. Immunotherapy is stopped permanently
5	Death related to adverse event	