Immunotherapy for Brain Tumors

John H. Sampson, Marcela V. Maus, and Carl H. June

ABSTRACT

Glioblastoma (GBM) is the most lethal form of brain tumor and remains a large, unmet medical need. This review focuses on recent advances in the neurosciences that converge with the broader field of immuno-oncology. Recent findings in neuroanatomy provide a basis for new approaches of cellular therapies for tumors that involve the CNS. The ultimate success of immunotherapy in the CNS will require improved imaging technologies and methods for analysis of the tumor microenvironment in patients with GBM. It is likely that combinatorial approaches with targeted immunotherapies will be required to exploit the vulnerabilities of GBM and other brain tumors.

INTRODUCTION

Recently, cancer immunotherapy has emerged as the first broadly successful strategy for a variety of cancers. The various approaches for cancer immunotherapy that are currently in clinical development or have reached Food and Drug Administration approval are listed in Table 1.

Antagonistic antibodies to the cytotoxic T-cell lymphocyte antigen-4 and programmed death 1 pathways have been approved for use in an increasing list of cancers, including melanoma, bladder, kidney, and non–small-cell lung cancers and Hodgkin lymphoma. An oncolytic herpesvirus was approved for the treatment of metastatic melanoma in 2016. In 2017, chimeric antigen receptor (CAR) T cells that target CD19 are expected to receive Food and Drug Administration approval for acute lymphoblastic leukemia and diffuse large-cell lymphoma. Here, we discuss the current challenges and opportunities for the development of immunotherapy for brain tumors. We also provide a brief overview of current approaches in the clinic. There are comprehensive reviews of immunotherapy for primary brain cancers.

However, the spontaneous occurrence of multiple sclerosis and other autoimmune syndromes that are mediated by the cellular immune system indicates that immunosurveillance by T cells occurs.

Paraneoplastic neurologic syndromes have long been known to clinicians, and they provide one of the clearest examples of naturally occurring tumor immunity and immunosurveillance of the CNS in humans. Conversely, severe immunosuppression can lead to viral reactivation in the CNS, as evidenced by the incidence of JC virus–induced progressive multifocal leukoencephalopathy in patients treated with rituximab or natalizumab. Animal models suggest that the breaking of peripheral tolerance and the occurrence of neurotoxicity can be uncoupled.

The brain was thought to be devoid of lymphatics, but recent studies show that lymphatics exist in the arachnoidal meninges and dura, and that lymphocytes exit the brain via this system to deep cervical lymph nodes. Thus, antigens and antigen-presenting cells from the brain parenchyma drain via dural lymphatics and from the cribriform plate to the cervical lymphatics.

In the healthy brain, resting T cells do not cross the blood-brain barrier but traffic from meningeal blood vessels into the CSF, where they can gain access to the brain parenchyma via the pia mater or choroid plexus. Thus, these studies indicate that, in principle, antigens that arise from tumor mutations should be visible to the immune system in the deep cervical lymph nodes and that T cells administered by systemic infusion would have access to tumors via the CSF and choroid plexus routes. Finally, to the degree to which these barriers limit access of immunotherapy
to the brain, direct infusion of antibodies and other drugs by convection-enhanced delivery and related methods provides a potential opportunity for direct drug delivery, which may then leverage these barriers to limit egress of these molecules.

Although allografts engraft and can avoid rejection for long periods in the rabbit brain, the rat brain is highly infiltrated by activated T cells within 12 hours after intravenous infusion. As such, T-cell therapies that use activated T cells, such as CAR T cells, should have minimal limitations in access to the brain. However, not all T cells have equal access to the brain. For example, autoreactive CD4+ T cells are first licensed in the lung, where they acquire expression of *Ninj2* and very late antigen 4, which facilitates later migration and entrance to the brain. Other data indicate that the leptomeninges represent a second checkpoint at which point-activated T cells also are licensed to enter the CNS parenchyma.

It is clear that the human nervous system is susceptible to life-threatening toxicity as a result of autoimmune attack. Historic work demonstrated that rodents and nonhuman primates vaccinated with brain tumor tissue and common adjuvants can succumb to fulminant autoimmune encephalitis. In these clinical observations and experimental studies, it remains unclear whether these toxicities are due to direct attack that is based on antigen expression or to the spread of the immune responses to other unrelated antigens. This differentiation has importance for the therapeutic approaches selected for this field. However, recent experiments with engineered T cells that have specificity for melanoma-associated antigen 3 show that direct toxicity from T cells in the absence of epitope spreading can be devastating: several patients developed necrotizing leukoencephalopathy as a result of cross-reaction with melanoma-associated antigen 12, an antigen expressed in the normal brain.

Epitope spreading commonly occurs in autoimmune disorders in the CNS. To the degree to which tumor-specific and nonhomogeneously expressed antigens are targeted, a highly specific approach may be safe if epitope spreading does not occur; paradoxically, it also may be ineffective because of antigen heterogeneity.

T cells specific for gliomas face a hostile tumor microenvironment in the CNS. Recent work by Chongsathidkit et al suggests that tumors in the CNS prevent T-cell immigration and induce sequestration of T cells in the bone marrow; this may be related to the lymphopenia observed in patients with gliomas even before they start lymphodepleting chemotherapies, such as temozolomide. In addition, glioma cells and their exosomes promote interleukin-10 (IL-10) and arginase-1 production and induce monocytes to convert to myeloid-derived suppressor cells. C-C motif chemokine ligand 2 produced by gliomas cells also recruits myeloid-derived suppressor cells and regulatory T cells.

In addition, indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase often are overexpressed in gliomas, and higher-grade gliomas express higher levels of indoleamine 2,3-dioxygenase than lower-grade gliomas do. These enzymes are part of tryptophan metabolism, and their upregulation results in increased production of the tryptophan catabolite kynurenine. Both tryptophan depletion and kynurenine are thought to be immunosuppressive to cytotoxic T cells.

Kynurenine also results in recruitment of immunosuppressive regulatory T cells, perhaps through changes in production of chemokines such as C-C motif chemokine ligand 2 or through its interaction with the aryl hydrocarbon receptor. The PD1 and programmed death ligand-1 axis also is active in gliomas, though results in the preclinical immunocompetent mouse models were more encouraging than what has been observed in early clinical trials.

Gliomas are heterogeneous tumors and identification of the immunologically relevant antigens is challenging. Most of the tumor-specific mutations, or neo-antigens, are unique to each individual. Gliomas are heterogeneous both among different patients and within each patient. These two forms of heterogeneity make targeted therapies, even immunologically based ones, such as vaccines and engineered T cells, challenging to develop for patient groups and for individual patients. Even in early trials of CAR T cells, antigen escape has occurred in both hematologic and solid tumor malignancies.

The ideal tumor antigen also would be expressed on the cancer stem cell and would have a role in the maintenance of the tumor phenotype. The epidermal growth factor receptor variant III antigen, for example, is a constitutively active oncogenic mutation, but it nevertheless is expressed only in approximately 30% of patients with glioblastoma (GBM), and its expression is heterogeneous subclonal mutations within each tumor. Human epidermal growth factor receptor 2 is expressed more frequently and homogenously, but its expression in other life-sustaining tissues may narrow the therapeutic window. IL-13 receptor α2 (IL-13Rα2) also is expressed frequently in GBM (approximately 58%), but is not essential for the tumor phenotype, and escape has been noted with both fusion ligands and T cells directed to it. Identification of single targets is difficult, but the reality is that, in the long run, multiple antigens will need to be targeted for most patients to have a reasonable expectation of clinical benefit. Studies of combined antigen-specific CAR T cells have been proposed to avoid antigen escape, and these studies are expected to enter clinical trials within the year. Checkpoint blockade alone or in combination with engineered T-cell therapies also may effectively overcome tumor heterogeneity, because multiple patient-specific mutations could be targeted at once, which would enhance the breadth of the antitumor immune response.
Many clinical trials are being conducted in GBM. Some of these are listed in Table 2.

**Checkpoint Inhibitors**

In preclinical murine models with orthotopic transplanted gliomas, checkpoint inhibitors have worked well individually and in combination with each other or other immunotherapy approaches.\(^39-43\) Ipilimumab and pembrolizumab have been shown to have acceptable safety and some efficacy in patients with metastatic brain metastasis from melanoma or non–small-cell lung cancer.\(^44,45\) Although recent clinical data suggest that the results with these approaches in patients may have some promise,\(^46-49\) the results clearly are not yet as dramatic as those seen in metastatic tumors within the brain or systemic tumors. This may relate to these tumors in general being cold tumors\(^50,51\)—that is, they lack a considerable amount of intratumoral inflammatory cells;\(^52\) however, these tumors do have some variability in this regard.\(^53\) The underwhelming results also may relate to the relatively low mutational rate of gliomas.\(^54,55\) Malignancies with a high burden of clonal neoantigens, such as those induced from chemotherapy,\(^54,56-58\) or tumors with high mismatch repair mutations,\(^59\) including gliomas,\(^60\) do seem to have a high response rate to checkpoint blockade.

It would be helpful to have more data about where therapeutic molecules must be located to have beneficial effects. Do the drugs, usually large antibodies that may have limited access to the brain because of the blood-brain barrier, need direct access to the CNS, or can they operate systemically by activating T cells that can then easily penetrate the brain? We still do not know the degree of penetration these molecules have to get into the brain to treat primary tumors, but the amount may be quite low.\(^61\) Novel approaches of delivery of these drugs that either deliver them directly into the brain\(^62\) or transport them in novel ways from the systemic circulation into the brain may yield more promising results.

**Vaccines**

A spectrum of vaccines has been used in preclinical and clinical studies against primary brain tumors.\(^63-74\) These vaccines have targeted normal or overexpressed tumor proteins within the tumor,\(^63-69\) proteins with specific amino acid changes that resulted from tumor-specific neo-epitopes,\(^72-74\) or viral antigens. The approaches used various antigen substrates, including peptides, full-length proteins, RNA, and DNA. Vaccines have consisted of the antigens alone; antigens in combination with various local\(^71\) or systemic adjuvants;\(^72\); or antigens used in the context of cell-based therapy, such as dendritic cell vaccines. None of these approaches have been optimized, and a comparison of nonoptimized regimens has not been useful to differentiate which approaches might be best.

To date, there is no phase III trial to demonstrate the efficacy of vaccines in any cancer except prostate cancer. Preclinical work in this regard, then, generally has failed to predict clinical results. This may be due to the use of heterogeneously expressed antigens, or the need for generation of different immune responses systemically to attack antigens within the CNS, or the need to alter the tumor microenvironment differently within the CNS for these vaccine approaches to be successful.\(^75\) One example of a study with a single antigen that is heterogeneously expressed in GBM as a target is the recent phase III ACT IV trial, although the study failed to support use of the single antigen. It is possible that vaccine approaches against tumor-specific antigens, which are more homogeneously expressed, such as the IDH1 or IDH2 mutations, may be more favorable.

More recently, vaccines that target epitopes that may be recognized by CD4+ T cells in the context of major histocompatibility complex class II presentation seem to have shown some promise in preclinical studies.\(^76,77\) However, the mechanism by which these would work in malignant gliomas, which may not express major histocompatibility complex class II (at least not de novo),\(^78\) is yet to be determined.

**Cellular Therapies**

The presence of lymphocytes within malignant gliomas can be a positive prognostic indicator of survival for patients with these tumors.\(^79,80\) However, such naturally existing T-cell responses are insufficient to mediate regression of gliomas and may be related to the lack of high-affinity T-cell receptors specific to glioma antigens, to checkpoint molecules, and to limitations in antigen presentation in the CNS.

**Synthetic Biology With Engineered T Cells**

Engineered T cells are part of a broad explosion in immunology. What perhaps makes these therapies most revolutionary, though, is the concept of use of a living cell as the therapeutic platform. Living T cells after genetic modification are radically different from inanimate platforms, such as small molecules or antibodies, in that the cells are capable of intelligent sensing and response behaviors. At the same time, these cells are more challenging to manipulate, manufacture, and control. In theory, the combination of a living platform that is capable of complex sensing and response behaviors with the ability to genetically reprogram these behaviors is what generates the disruptive therapeutic potential of this approach.

Adaptive immunotherapy with redirected T cells obviates the need for antigen presentation and stimulation of a primary immune response and can be directed to specific antigens with well-characterized, high-affinity antigen receptors. T cells redirected with CARs that target the B-cell marker CD19 have shown remarkable and durable efficacy in acute lymphoblastic leukemia, chronic lymphocytic leukemia, and B-cell lymphomas.\(^81-87\) Most CARs are designs to target surface proteins or antigens independent of HLA. One of the principal challenges in the development of new CARs is identification of an appropriate cell surface antigen to target. The principal antigens that have been targeted with such HLA-independent CARs include human epidermal growth factor receptor 2/neu,\(^88\) IL-13R\(_a_2,\)^\(^35,89\) and epidermal growth factor receptor variant III\(^90,91\); there is also interest in ephrin-A2—targeted CAR development, but these CARs have not yet entered clinical trials.\(^92\)

In addition to targeting multiple antigens, there are many other variables to consider in the design and administration of...
<table>
<thead>
<tr>
<th>Immunotherapy Approach and Agent</th>
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<td>corresponding to IL-13Rα2 and surviving</td>
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<td><strong>Adoptive T cell</strong></td>
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<td>CAR T EGFRvIII</td>
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<td>CMV CAR T HER2</td>
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<td>Donor NK cells</td>
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<td>NCT02100891</td>
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Note: Identifiers and titles obtained from clinicaltrials.gov access on February 1, 2017. Abbreviations: BTSC, brain tumor stem cells; CAR, chimeric antigen receptor; CART133, CAR T cell CD133; CMV, cytomegalovirus; CTLs, cytotoxic T lymphocytes; DCs, dendritic cells; DCVax-L, Dendritic Cells Pulsed With Tumor Lysate Antigen; EGFRvIII, epidermal growth factor receptor variant III; GBM, glioblastoma; GM-CSF, granulocyte-macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; HSCs, hematopoietic stem cells; ICLC, polynosinic-polycytidylic acid and poly-L-lysine double-stranded RNA; IDH1, isocitrate dehydrogenase 1; IDH1R132H, IDH1 R132H point mutation; IL-13Rα2, interleukin-13 receptor α2; LAG-3, lymphocyte-activation gene 3; LAMP, lysosome-associated membrane glycoprotein; MGMT, methylguanine methyltransferase; MRI, magnetic resonance imaging; NK, natural killer; NSCLC, nonsmall-cell lung cancer; NY-ESO-1, cancer testis antigen CTAG1B gene product; PD-1, programmed death 1; PD-L1, programmed death ligand-1; STIR, Solid Tumor Immunotherapy Response; TGF-βRI, transforming growth factor β receptor 1; xALT, ex vivo expanded autologous lymphocyte transfer.
cellular therapy with engineered T cells. The CARs may contain different signaling domains, which can affect their long-term proliferation and survival; they may be cultured differently during the ex vivo manufacturing process; and the vectors used to introduce and maintain CAR expression may affect the T-cell biology.93 Brown et al93 recently reported a striking response in a patient with a poor prognosis of multifocal GB after multiple intraventricular infusions of IL-13Rα2 CAR T cells.94 This raises the possibility that local delivery of CAR T cells may enhance response in GBM and that the route of administration is important, as suggested by preclinical studies in mesothelioma.94

In conclusion, the advances in general oncology coupled with the recent fundamental advances in the understanding of neuroimmunology have created opportunities for the development of effective immunotherapy for malignant brain cancer. It is likely that combinatorial regimens with complementary mechanisms of action will be required to achieve a broad and durable antitumor benefit. Previous experience indicates that there are considerable challenges in the translation of early-stage trials to trials that change the standard of care.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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