Immunotherapy for Glioma
Promises and Challenges

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KEYWORDS

• Glioma • Glioblastoma multiforme • Brain tumors • Central nervous system • Immunotherapy
• Cytokines • B cells • T cells

KEY POINTS

- High-grade gliomas (glioblastoma multiforme) are the most common primary intracranial neoplasms and are associated with a poor prognosis, despite the current standard of care treatment (surgical resection, followed by radiation and temozolomide chemotherapy).
- There is active research investigating novel immunotherapies in the treatment of high-grade gliomas.
- Gliomas suppress immune function in the brain by limiting effective communication with immune cells, secreting immune-inhibitory cytokines and molecules, and expressing molecules that induce apoptosis of immune cells.
- To combat tumor-associated immunosuppression, there are 3 categories of immunotherapeutic approaches: cytokine immunotherapy, passive immunotherapy (including serotherapy and adoptive immunotherapy), and active immunotherapy.
- Although immunotherapeutic approaches have met with mixed success so far, immunotherapy continues to be actively pursued because of its potential to harness the potency, specificity, and memory of the immune system to attack infiltrating high-grade gliomas.

INTRODUCTION

The most common primary brain neoplasm, glioblastoma multiforme (GBM), is associated with a dismal prognosis. With the standard of care treatment regimen of aggressive surgical resection, radiation, and chemotherapy, the median survival remains only 14 months.[1] However, advances in conventional treatments (ie, radiation and chemotherapy) have brought only modest improvements in patient survival. As a result, new treatment modalities, such as immunotherapy, are being pursued.[2] This article describes the current strategies and results of immunotherapy for high-grade gliomas.

The central nervous system (CNS) has historically been considered an immune-privileged organ in which immune activity is significantly decreased.[3] Several unique anatomic and physiologic characteristics limit immune surveillance and response in the brain.[4] First, the CNS lacks a lymphatic system. Second, the brain is shielded from the peripheral circulatory system by the blood-brain barrier (BBB), and is therefore isolated from most peripheral immune cells, soluble factors, and plasma proteins. Third, the brain has high levels of immunoregulatory cells and factors that decrease immune function. Fourth, CNS cells express low baseline levels of major histocompatibility complex (MHC) molecules

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responsible for antigen presentation to immune effector cells.[5]

Despite these factors, effective immune responses are performed in the CNS. Both the complement system[6] and the antigen-antibody system, including functional B cells,[7,8] are active in the CNS. In response to insults, CNS antigen-presenting cells (APCs), microglia, are activated, upregulate MHC and costimulatory molecules, and stimulate CD4-specific and CD8-specific T cell responses.[9–11] A small number of lymphocytes are found in normal, healthy brain,[12] and both naive lymphocytes[13] and activated T cells can cross the BBB.[12,14,15] Many different types of lymphocytes also infiltrate the CNS in the presence of disease, such as gliomas.[16–19] However, the magnitude and potency of these immune response in the CNS remain to be elucidated.[15]

TUMOR-ASSOCIATED IMMUNOSUPPRESSION

In addition to the classic hallmarks of cancer, gliomas display an additional unique feature: the ability to evade and suppress the immune system in various ways.[20] First, by limiting effective signaling between glioma and immune cells (by either expressing low levels or defective human leukocyte antigen [HLA]), glioma cells evade immune detection. A recent study by Facoetti and colleagues[21] found that approximately 50% of 47 glioma samples displayed loss of the HLA type I antigen, and a high proportion of these showed selective loss of HLA-A2 antigen as well. Loss of HLA type I antigen was more common among higher-grade tumors, suggesting a role of deficient antigen presentation in glioma progression.

Inhibition of antigen presentation by microglia and macrophages in the tumor microenvironment also contributes to the tumors' ability to escape immune detection. In vitro, the presence of glioma cells induces monocytes to reduce their phagocytic activity.[22] In addition, microglia within glioma tissue are deficient in proper antigen presentation for cytotoxic and helper T cell activation,[23] with, for example, significantly less MHC-II induction by microglia and macrophages from gliomas compared with normal brain tissue.[24] Stimulation of microglia in the presence of tumor cells also reduces the secretion of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, but increases the secretion of the inhibitory cytokine interleukin (IL)-10.[25]

The lymphocytic population is also altered in the presence of gliomas. CD4+ helper T cells have depressed function in both the peripheral blood and tumor microenvironment,[26,27] display weak proliferative responses, and produce lowered amounts of the T_H1 cytokine IL-2.[28] Most CD8+ T cells are not activated.[29] In patients with malignant gliomas, a subpopulation of T lymphocytes termed T regulatory cells (T_{reg}; eg, CD4+CD25+ cells) that suppresses activity of effector T cells is increased.[21,24,30–32] By downregulating the production of key cytokines, such as IL-2[33] and interferon (IFN)-γ[34,35] from target lymphocytes, these T_{regs} potently inhibit T cell activation, proliferation, and differentiation.[33] In vivo experiments have shown significantly improved survival after depleting T_{regs} in a murine model of glioma (GL261) by injecting an anti-T_{reg} antibody (anti-CD25+ monoclonal antibody [mAb]).[36,37]

Gliomas secrete various immune-inhibitory cytokines, such as IL-10,[38] and other immunomodulating molecules that play an important role in glioma-associated immunosuppression. Malignant glioma cells produce large amounts of prostaglandin E2,[39,40] which, in turn, inhibits IL-2 activation of lymphocytes.[41,42] They also express high levels of TGF-β2,[41,43] which is also known as glioblastoma cell–derived T cell suppressor factor (G-TsF) because of its potent inhibition of cytotoxic T cells.[44–46] Inhibition of signaling through the TGF-β2 pathway by antisense RNA in the C6 rat glioma model significantly prolonged survival[47] and, at times, eradicated the tumor.[48] These experiments strongly support the key role that TGF-β2 plays in the immunosuppression that seems essential for the survival of glioblastoma cells.

In addition to secreting immunosuppressive factors, glioma cells also express molecules that induce apoptosis of immune effectors, such as Fas ligand (FasL), galectin-1, and B7-H1, further contributing to their immunosuppressive properties.[49,50] FasL and its receptor Fas are important mediators of apoptosis in the immune system, particularly of CD8+ cytotoxic lymphocytes. High expression of FasL by human glioma cells is associated with low levels of T cell infiltration,[51] suggesting that FasL expression by tumor cells may contribute to T cell depletion in tumors by increased T cell apoptosis. However, the clinical significance of FasL expression levels remains to be determined. Like Fas/FasL, galectin-1 induces apoptosis in a variety of immune cell types through an alternate signaling pathway.[52] Overexpression of galectin-1 by gliomas[53] likely also contributes to increased apoptosis of T cells by gliomas, serving as another method of evasion from the antitumor activity of T lymphocytes. B7-H1 is a potent immunosuppressive surface molecule that induces T cell apoptosis via the PD-1 signaling pathway and is overexpressed in a subset of gliomas with particularly strong immunoresistant phenotypes.[50] Not only the glioma cells but also

microglia in the presence of gliomas have increased levels of 2 of these proapoptotic factors, FasL and B7-H1.[54–56]

In addition, iatrogenic factors may cause systemic immunosuppression in patients with gliomas. Corticosteroids prescribed for tumor-associated edema may inhibit cytokine production and sequestration of CD4+ T cells.[57] However, recent evidence suggests that, at therapeutic doses, corticosteroids do not interfere with immunotherapy.[58] In addition, chemotherapeutic agents, such as temozolomide, can cause lymphopenia, particularly of the CD4+ population,[59] which may weaken the effect of immunotherapeutic modalities that depend on the CD4+ T cell response. Other chemotherapeutic agents, such as rapamycin, inhibit production of the proliferative cytokine IL-2[57] and may therefore exacerbate the immunosuppressive state in patients with high-grade gliomas.

IMMUNOTHERAPY

The major challenge in the management of malignant gliomas has been the inevitable recurrence of the tumor despite aggressive therapy. This problem highlights the infiltrative nature of high-grade gliomas, which have often already spread with evidence of diffuse microscopic disease beyond the tumor mass at the time of clinical presentation. The development of a successful mode of therapy requires systemic efficacy throughout the brain, with the ability to target tumor cells left behind after surgical resection and conventional adjuvant therapies. Such systemic therapy must also be highly specific for infiltrating tumor cells. Immunotherapy represents a promising modality, with the potential to harness the potency, specificity, and memory of the immune system to attack infiltrating glioma cells.

The main strategies in anti-glioma immunotherapy include cytokine therapy, passive immunotherapy, and active immunotherapy. Cytokine therapy is based on the concept that administration of immunomodulatory cytokines activates the immune system. Passive immunotherapy includes serotherapy, in which monoclonal antibodies are given to aid in immune recognition of tumor and to deliver toxins to tumor cells, and adoptive therapy, which involves tumor-specific immune cells that are expanded ex vivo and reintroduced to the patient. Active immunotherapy involves generating or augmenting the patient's own immune response to tumor antigens, typically by administrating tumor antigens or professional APCs.

Cytokine Therapy

Cytokines are potent immunomodulators, and immunotherapy with cytokines has been applied in oncology against a variety of tumors with variable success. To deliver cytokines to the CNS, different strategies have been explored, including injection/infusion of recombinant cytokines, vectors containing cytokine-encoding genes, cells that secrete cytokines, or cytokines linked to toxins.

The first clinical trial using cytokine immunotherapy showed promising results using intratumoral IFN-α in addition to surgery and radiotherapy,[60] but the study was limited by design flaws.[20] In contrast, Farkkila and colleagues[61] found that their IFN-γ neoadjuvant and adjuvant to radiotherapy regimen was well tolerated but did not offer a statistically significant survival benefit. Follow-up studies using systemic or intrathecal administration of IFN-α, IFN-γ, and/or IL-2 continued to find no significant improvement in survival, and patients in the treatment arm encountered considerable toxicities.[62–64] Current research is addressing improved targeting of cytokine delivery to reduce systemic toxicity and increase the effective cytokine concentrations within the tumor.

Viral vectors for local delivery of cytokines to glioma cells met with only limited success.[65–67] However, strategies using intratumoral implantation of various cell types genetically modified to produce cytokines produced more encouraging results. Injection of IL-2–secreting allogeneic fibroblasts into GL261 tumors in mice significantly delayed tumor development when injected before the tumor cells and prolonged survival in mice with established tumors.[68–70] Injection of neural stem/progenitor cells (which are attractive carrier cells because they can self-replicate, have prolonged survival, and migrate long distances) transfected to produce IL-2,[71] IL-4,[72] IL-12,[73] and IL-23,[74] improved survival in animals with established gliomas.

Alternate vehicles for intratumoral cytokine delivery include liposomes and biopolymer microspheres. Injection of liposomes containing a plasmid with the IFN-β gene into GL261 gliomas in mice induced a robust activation of natural killer cells,[75] IFN-β expression by tumor cells, significant infiltration of cytotoxic T cells, a 16-fold reduction in mean tumor volume, and a complete response in 40% of animals.[76] Biopolymer microspheres containing IL-2 were also effective in generating a specific response when injected into mice and rat gliomas.[77–79]

Cytokines have also been used to deliver toxins, such as *Pseudomonas* exotoxin, to attack glioma cells. Cytotoxic effects of *Pseudomonas* exotoxin conjugated to IL-4 (whose receptor is highly expressed on glioma but not normal brain cells[80,81]) against glioma cells have been shown in vitro.[81,82]

In the clinical trial of intratumoral injection of IL-4-*Pseudomonas* exotoxin for patients with high-grade glioma, 6 out of 9 patients showed evidence of tumor necrosis, with no significant toxicity found in any patient.[83] Clinical trials are currently underway to evaluate this modality's efficacy and maximum tolerated dose.[84,85]

Intratumoral injections of *Pseudomonas* exotoxin conjugated to IL-13R (which is similarly overexpressed in malignant gliomas[86–88]) is well tolerated in patients with recurrent malignant glioma.[89–91] Recent efforts have focused on optimizing the specificity and strength of the interaction between IL-13 and IL-13R of glioma cells,[92] as well as developing new modes to deliver the IL-toxin.[93] *Pseudomonas* exotoxin conjugated to TGF-α has also shown improvement in survival of mice bearing tumor xenografts, with greater improvements seen in mice that express the epidermal growth factor receptor (EGFR).[94,95] In a phase I clinical trial, 2 patients received intratumoral infusions of TGF-α conjugated to the *Pseudomonas* exotoxin and showed radiographic response with relative safety.[96]

Overall, immunotherapy with cytokines has shown safety, with variable efficacy. Thus, given the relative nonspecificity of cytokine therapy, it may prove most useful as an adjunct to other types of therapies. The potential use of cytokines as an adjunct to chemotherapy, termed chemoimmunotherapy, is an active area of development.[79,97]

Passive Immunotherapy

Serotherapy

Passive immunotherapy includes serotherapy and adoptive immunotherapy. Serotherapy uses monoclonal antibodies to effect an antitumor response or to achieve specific delivery of toxins, chemotherapy, or radiotherapy to tumor cells. An important determinant of its success is the identification of glioma-specific antigens (ie, specific antigens that are expressed on glioma cell surfaces but not on normal brain parenchyma). Targeted glioma antigens have included tenascin, EGFR and its mutated form EGFRvIII, chondroitin sulfate, vascular endothelial growth factor (VEGF) receptor, neural cell adhesion molecule (NCAM),[98] and hepatocyte growth factor/scatter factor.[99]

An extracellular matrix protein strongly expressed in gliomas but not normal brain, tenascin, is readily identified immunohistochemically by mAb 81C6.[100] Systemic administration of ^{131}I-conjugated 81C6 mAb to mice with human glioblastoma xenografts prolonged survival,[101,102] with evidence of radioisotope localization to the tumor.[103] Clinical trials of ^{131}I-conjugated 81C6 mAb given intrathecally have shown safety at low radiation doses, with neurotoxicity and hematologic toxicity at higher doses.[104–106] Several phase I and II trials studying ^{131}I-conjugated 81C6 mAb injected into the surgical resection cavity in humans with glioblastoma have shown improved survival.[104,107–112]

Similar to tenascin, EGFR is specifically overexpressed by glioma cells, and signaling through EGFR is thought to play a key role in survival, proliferation, and progression of gliomas. In a clinical trial by Kalofonos and colleagues,[113] patients with high-grade gliomas were treated with ^{131}I-conjugated mAb to EGFR injected intravenously or infused into the internal carotid artery, with 6 out of 10 patients showing clinical response lasting 6 months to 3 years and no major toxicity. In another trial, a single intravenous injection of murine anti-EGFR mAb, EMD55900 (mAb 425), was given to 30 patients with malignant gliomas, showing binding of EMD55900 to the tumor in 73% of patients.[114] In a phase I/II study in which patients were given repeated infusions of EMD55900, toxicity was minimal, but no significant therapeutic benefit was found, because 46% of patients had progressed at 3 months.[115] Another trial using EMD55900 was stopped because of high levels of toxicity of inflammatory reactions.[116]

Several other phase I, II, and III trials have been conducted using EMD55900 conjugated to ^{125}iodine,[117–120] showing that the conjugated mAb localizes to the glioma and is well tolerated. Two phase II trials in which patients received radiolabeled mAb following standard resection and radiation therapy showed a median survival of 15.6 months[119] and 13.5 months respectively.[120] Phase III trials are currently ongoing.[117] Another trial, which used a humanized anti-EGFR antibody, h-R3, designed to inhibit the kinase activity of the EGFR receptor, showed no high-grade toxicity and an overall 38% response rate, with stable disease in 41% patients at a median follow-up of 29 months.[121]

EGFRvIII is a constitutively active mutant form of EGFR and, as a tumor antigen that likely has a large role in tumorigenicity, is an attractive target for serotherapy.[122] Systemic injections of the anti-EGFRvIII mAb 806 into mice with U87 glioma xenografts significantly reduced tumor volume and increased survival.[123]

These EGFR and EGFRvIII antibodies can provide specific targeted delivery of chemotherapeutics or toxins to glioma cells as well. Mamot and colleagues[124] used fragments of mAbs binding EGFR and EGFRvIII conjugated to immunoliposomes containing the cytotoxic drugs doxorubicin, vinorelbine, and methotrexate and observed successful intracellar delivery of these drugs to glioblastoma cells in vitro. They then

showed efficacy in slowing tumor growth of EGFR-targeted immunoliposomes containing cetuximab in mouse xenograft models.[125] Antibodies have also been conjugated to several different toxins, with varying results.[126] The specificity of delivery of therapeutic agents by monoclonal antibodies to tumor-specific antigens holds great potential for limiting therapeutic toxicity in immunotherapy against gliomas.

Adoptive immunotherapy

Adoptive immunotherapy augments the antitumor response with the reintroduction of immune effector cells that have been isolated from the patient and expanded ex vivo under controlled conditions. Most adoptive immunotherapeutic strategies have used harvested lymphocytes stimulated with IL-2 to produce lymphokine-activated killer cells (LAKs). Others have used tumor-infiltrating lymphocytes; neural stem cells (discussed earlier), tumor-draining lymph node T cells; and non–MHC-restricted, cytotoxic T cell leukemic cell lines.

Jacobs and colleagues[127] reported the first clinical trial studying immunotherapy with LAKs. LAKs and IL-2 were infused directly into the tumor bed of patients with malignant glioma, with minimal toxicity,[128] and mean progression-free survival in this small cohort was 25 weeks.[129] Other trials using this technique found a small benefit in patient survival, but showed dose-limiting neural toxicity related to IL-2-induced cerebral edema.[130–132] A recent study by Dillman and colleagues[133] reported a median survival of 17.5 months in patients with GBM who had LAKs placed in the resection cavity, compared with 13.6 months in controls. In mouse models, LAKs coated with bispecific anti-CD3 and anti-glioma antibodies increase the LAK activity of peripheral blood lymphocytes against the xenograft gliomas.[134] The tumor-bed infusion of these coated LAKs in clinical trials showed promising results, with either partial or complete radiographic glioma regression in 8 of 10 patients.[135] None of the 10 patients suffered tumor recurrence during follow-up of 10 to 18 months, and 9 of the 10 control patients given untreated LAK cells developed recurrent tumor within 1 year.[135]

Tumor-infiltrating lymphocytes (TILs) found within glioma tissue contain a higher proportion of cytotoxic CD8+ T cells compared with peripheral blood. Because they are readily expanded in culture, presumably recognize 1 or more tumor antigens, and are much more cytotoxic to glioma cells than LAKs,[136] TILs are promising candidates for adoptive immunotherapy. In the GL261 murine glioma model, TILs were incubated with enzymatically digested GL261 cells and IL-2 and then infused intraperitoneally into mice harboring gliomas in the liver or brain.[137] The infusion reduced the number of liver metastases but did not lengthen the survival of animals with GL261 tumors in the brain, leading the investigators to conclude that the inefficacy of TIL therapy in the brain reflects the unique challenges of the immunosuppressive tumor microenvironment and that more efficient delivery systems need to be developed.[137] However, subsequent studies have reported success with TILs in treatment of intracranial gliomas in vitro.[138,139] Several clinical pilot studies have described the feasibility of reinfusion of IL-2 and autologous TILs expanded in vitro to patients systemically and locally with little toxicity,[140,141] but evidence for the efficacy of such a technique is currently lacking. Despite the drawbacks of TILs (including altered cellular signaling, decreased proliferation, defective cytokine secretion, decreased cytotoxic capacity, and a predisposition toward apoptosis[40,142–145]), the superior specificity of TILs compared with LAKs and early clinical success with TIL strategies warrant further investigation.

The use of tumor-draining lymph node T cells and non–MHC-restricted, cytotoxic T cell leukemic cell lines has also been explored. In a phase I trial, 12 patients with astrocytoma, anaplastic glioma, or GBM were initially given injections of T lymphocytes from tumor site–draining lymph nodes after activation and expansion ex vivo.[146] Partial regression was observed in 4 patients, and no long-term toxicity was seen during the 2-year follow-up period.[146] In another study, transfer of TALL-104 cells (non–MHC-restricted cytotoxic T cells derived from a patient with acute T-lymphoblastic leukemia) into tumor sites of U87 xenografts in mice significantly reduced tumor growth[147] and prolonged survival[148] by both direct tumoricidal action and recruitment of endogenous antitumor activity.[149] Geoerger and colleagues[150] subsequently showed evidence of significant cytotoxic activity of TALL-104 cells against several human glioblastoma cell lines in rat models, and stressed the importance of local, as opposed to systemic, administration of TALL-104 cells. Preclinical studies have characterized the cytotoxic activity, trafficking patterns, viability of TALL-104 cells under different conditions, and specific activity against brain tumor cells, concluding that TALL-104 cells are appropriate for human clinical trials.[151,152] TALL-104 implantation therapy shows killing of glioma cells, but not of normal brain cells, through a mechanism mediated by specific cytokine release, and their activity is not altered by the presence of radiotherapy or corticosteroids.[151]

In summary, like cytokine therapy, adoptive immunotherapy (using LAKs, TILs, or the other

cell types discussed earlier) is not fully effective by itself, but may become an important adjuvant to standard treatments and other immunotherapies for primary gliomas.

Active Immunotherapy

Active immunotherapy involves priming or augmenting patients' immunity in vivo by vaccinating against tumor antigen. Tumor vaccines for malignant glioma have been the focus of great interest in recent years. However, successful development of glioma vaccines requires proper presentation of tumor antigens and induction of an effective, durable, antigen-specific T cell immune response. Early efforts in active immunotherapy used vaccines containing autologous tumor cells as a source of glioma tumor antigens, given with various cytokines for immune stimulation.[153–156] Despite evidence for the safety and feasibility of such techniques, many challenges in glioma vaccine development remain because of the innately poor antigen-presenting capacity of glioma tumor cells, with low levels of expressed costimulatory molecules.

To augment antigen presentation, professional APCs have been used in glioma vaccines. Recent interest has turned to dendritic cells (DCs), which have an abundant expression of costimulatory molecules and a great capacity for activating T lymphocytes. DCs that are exposed to tumor antigens are then used to initiate an antitumor response in the patient's endogenous T cells,[157] inducing T cell proliferation and generating cytotoxic responses in vitro.[158,159]

In clinical trials, autologous DCs are obtained from peripheral blood mononuclear cells or bone marrow, primed to maturation, exposed to tumor antigen in a variety of ways (including whole tumor cells, isolated peptides, tumor lysates,[160,161] or tumor RNA[161]), and then reintroduced to the patient. An early phase I trial used peptide-pulsed DCs isolated from peripheral blood and showed the generation of robust T cell infiltration into the tumor.[162] Initial efforts by Kikuchi and colleagues[163] used DCs fused to glioma cells and injected intradermally into patients with malignant gliomas. There were no adverse reactions, but a partial response in only 2 out of 8 patients was observed.[163] In a subsequent study by the same investigators, IL-12 was added to the formulation, and a more robust 50% radiographic tumor reduction was seen in 4 of 15 patients, with similar safety profiles.[164] A complete regression of glioma was achieved in the murine GL261 model when a regimen of intrasplenic vaccination with DC/tumor fused cells, local cranial radiotherapy, and anti-CD134 mAb 7 was given.[165] Liau and colleagues[166] proposed that the most promising patient subgroup for DC vaccine therapy may be patients with small, quiescent tumors with low expression of tumor TGF-β. The phase II randomized trial using tumor lysate–pulsed DC vaccine for high-grade gliomas is ongoing.

The use of unselected tumor extracts to prime DCs in such nonspecific ways risks inducing autoimmunity against antigens of normal brain.[167] In efforts to avoid this potential hazard, focus has turned to more specific approaches using tumor-specific antigens, such as EGFRvIII, as targets for glioma vaccines. Preliminary studies using EGFRvIII peptide–pulsed DCs showed generation of cytotoxic activity against the U87 human glioma cell line.[168] A phase I trial using an EGFRvIII peptide–based vaccine showed that the therapy was well tolerated, with treated patients with GBM having a progression-free survival of 6.8 months and a median overall survival of 18.7 months from vaccination.[169] The phase II/III randomized trial of the EGFRvIII peptide vaccine with radiation and temozolomide is ongoing.

Another peptide-based vaccine currently under study is based on heat shock protein gp96 and its associated peptides isolated from patient's autologous tumor acquired at the time of surgery.[170–172] Preliminary results of the ongoing phase I/II trial have shown the vaccine to be well tolerated, with evidence of induction of tumor-specific responses.

Infectious agents have also been used to induce an antigen-specific immune response to gliomas. These vaccines contain viral or bacterial vectors that carry tumor antigen genes, and are based on the premise that an immune response to the highly immunogenic infectious agent should augment the response to the tumor antigen as well. Such an approach using *Listeria monocytogenes* has shown efficacy against extracranial but not intracranial tumors in animal models, suggesting the potential for efficacy in gliomas with improved delivery systems to the CNS.[173,174]

MULTIMODALITY IMMUNOTHERAPY

To enhance the effects of immunotherapy in combating high-grade gliomas, combinations of the approaches discussed earlier (cytokine therapy, passive and active immunotherapy) have been attempted. Cytokine and active immunotherapy strategies have been combined by introducing tumor cells or fibroblasts transfected to produce cytokines, such as IL-2, IL-4, IL-12, IL-18, IFN-α, and GM-CSF, alone or in combination with DCs.[16,175–178] Several studies suggest

the promise of this strategy. Intratumoral administration of IL-2–producing tumor cells along with recombinant IL-12 significantly prolonged survival in mice with gliomas.[179] Tumor cells producing GM-CSF and/or B7-2, a costimulatory molecule, also increased survival in mice when injected locally into GBM.[180] In rat models, when complementary DNA (cDNA) of IFN-γ,[181] TNF-α,[67] and IL-4[182] was delivered retrovirally to glioma cells in situ, a strong immune response was generated and the established tumors were eliminated.

SUMMARY

The continued poor prognosis of patients with high-grade gliomas with current treatment protocols warrants new therapeutic approaches. Advanced-stage clinical trials of several promising immunotherapies are currently underway, and their results will determine the clinical value of these modalities. However, the challenges to immunotherapy remain numerous. Although immunotherapy and chemotherapy can potentially serve as coadjuvants, the current practice of administering temozolomide during and 6 months after radiation therapy interferes with the clinical testing of immunotherapies, which may be compromised both by concurrent chemotherapy and by the immunosuppression that accrues with time.

Another impediment to developing effective immunotherapy is the immunosuppressive characteristics that are the hallmark of malignant gliomas. Effective therapeutic strategies require overcoming these mechanisms by augmenting tumor antigen presentation, perhaps in a setting isolated from the tumor microenvironment. The heterogeneity of potential glioma antigens warrants research and investigation of multiple tumor-specific antigen targets. The optimal immunotherapy will likely use several of the strategies reviewed earlier and become a standard component of a combined multimodal approach to malignant gliomas.

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