Clinical Trials with Immunotherapy for High-Grade Glioma

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KEYWORDS

• High-grade gliomas • Immunotherapy • Clinical trials • Vaccines

KEY POINTS

- Current strategies for immunotherapy against high-grade glioma include adoptive immunotherapy, active immunotherapy, and immunomodulation.
- Early clinical trials suggest that immunotherapy is safe and beneficial in a subset of patients.
- Major biologic challenges that must be overcome for immunotherapy to succeed include immune-editing, decreased antigen presentation by glioma cells, and decreased immune cell activation.
- The difficulty in predicting the success of immunotherapy trials as well as comparing the results across studies is the heterogeneous nature of immunotherapy trial design and reporting.

INTRODUCTION

High-grade gliomas (HGGs, World Health Organization [WHO] grade III and IV) make up most primary brain tumor diagnoses, with an incidence currently estimated at 14,000 new diagnoses per year.[1] These tumors are associated with high morbidity and mortality and a median survival of 2 to 5 years[2,3] for patients with anaplastic astrocytomas (WHO grade III) and 14.6 months[4] for patients with glioblastoma multiforme (GBM, WHO grade IV).

The current standard of care for patients with HGGs is summarized in **Table 1**, and includes maximal surgical resection followed by adjuvant chemotherapy and radiation therapy. In patients with anaplastic astrocytoma, a clear standard of care is lacking. The current treatment strategy typically includes maximal surgical resection in combination with adjuvant radiation with or without temozolomide (TMZ).[4–10] Advances in imaging, neuronavigation, and fluoroscopic guidance[11] have improved safety, decreased deficits associated with surgery, and allowed for more complete tumor resection, with more accurate surgical margins. Furthermore, medical treatment is often required to treat tumor-associated signs and symptoms, including seizures, edema, fatigue, and cognitive dysfunction.[12] These treatments carry their own set of side effects, which must be managed alongside side effects from radiation and chemotherapy.

Despite advances in surgical and medical management of HGGs, there is no current treatment that specifically targets tumor cells and spares normal brain parenchyma. Recently, immunotherapy has emerged as a promising treatment strategy against intracranial tumors. Although the brain has historically been considered immune-privileged, more recent evidence suggests that the immune system is capable of effecting vigorous responses in the central nervous system (CNS). Microglia are considered the first line of defense in the brain and possess the ability to phagocytose foreign cellular material and synthesize proinflammatory cytokines and chemokines.[13] Several

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Table 1
Summary of standard treatments for HGGs

Tumor	Treatment Paradigm
Anaplastic astrocytoma (WHO grade III)	Maximal surgical resection with the option of adjuvant radiation, TMZ, or combination radiation and TMZ
GBM (WHO grade IV)	Maximal surgical resection with adjuvant radiation therapy and TMZ or Gliadel (Eisai Inc, NC, USA) (implanted carmustine wafers)
Recurrent primary brain tumor	Resection of recurrent lesion, with adjuvant Gliadel placement, chemotherapy, or experimental treatments

groups have shown that lymphocytes and antigen-presenting cells (APCs), including macrophages and dendritic cells (DCs), are able to cross the blood-brain barrier and migrate to tumor within the brain parenchyma.[14–19] However, despite the ability of immune cells to traffic into intracranial lesions, the cells are generally unable to eradicate the primary tumor, in part because of the presence of an immunosuppressive tumor milieu. The release of immunosuppressive cytokines into the tumor microenvironment,[20,21] activation of immune checkpoints,[22,23] and an enriched population of CD4+CD25+FoxP3+ T regulatory (T_{reg}) cells[22] and T_H17 cells[24,25] are implicated in preventing an aggressive antitumor immune response.

Despite these challenges, immunotherapy has the potential to be advantageous over other chemotherapeutic strategies because of the potential for cellular level specificity and long-term surveillance. The potential of immunotherapy against cancers has recently been highlighted with the approval by the US Food and Drug Administration (FDA) of sipuleucel-T for treatment of castration-resistant prostate cancer[26] and ipilimumab for unresectable or metastatic melanoma.[27] There is no FDA-approved immunotherapy for HGGs, but the clinical evidence, as described later, suggests that immunotherapy may be a useful strategy to combat HGGs. This article reviews several strategies, including adoptive immunotherapy, active immunotherapy, and immunomodulation, that have been tested or are currently being tested in clinical trials as of August, 2011.

ADOPTIVE IMMUNOTHERAPY

Adoptive immunotherapy is a strategy in which immune cells are taken from the patient and activated ex vivo against tumor-specific antigens. The activated lymphocytes are then reintroduced into the patient, either directly into the tumor cavity or systemically.

Lymphokine-Activated Killer Cells

Lymphokine-activated killer (LAK) cells are peripheral lymphocytes that are cultured with interleukin 2 (IL-2) ex vivo. Once reintroduced, these cells possess cytotoxic abilities, but require activation against tumor cell antigens by host APCs. LAK cells have been studied in clinical trials and have been shown to be associated with varying levels of toxicity and antitumor activity.[28–33] In a study by Hayes and colleagues,[28] LAK cells were delivered via Ommaya reservoir 5 times every 2 weeks for 6 weeks, resulting in a median survival of 12.2 months compared with a median survival of 6.2 months in contemporary patients with recurrent GBM who were treated with surgery and chemotherapy. A similar trial in recurrent GBM showed a median survival of 9 months and a 1-year survival of 34%.[34] The most recent clinical trial in primary GBM, reported by Dillman and colleagues,[35] showed that introducing LAK cells into the tumor cavity in which patients who had undergone standard of care (radiation and TMZ) was safe and resulted in a median survival of 20.5 months with a 1-year survival rate of 75%. The use of corticosteroids was associated with lower total LAK count and worse survival. These trials are summarized in **Table 2**.

Cytotoxic T Cells

Other methods of adoptive immunotherapy for HGGs include infusion of cytotoxic T lymphocytes (CTL) that are isolated from a patient's own tissues, including peripheral blood mononuclear cells (PBMC),[36–38] tumor-infiltrating T lymphocytes (TILs),[18] draining lymph nodes, or PBMCs after vaccination with irradiated autologous tumor cells (ATCs).

Five studies were completed using CTLs isolated from PBMCs and TILs. Results from these 5 phase I/pilot studies showed that this strategy was safe and associated with only minor toxicities, including isolated side effects of hemorrhage and fever,[37] and transient cerebral edema in patients receiving TILs.[18] In each of these studies, the CTLs that were activated ex vivo were injected directly to the tumor cavity.