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.

Table 2
Immunotherapy trials using LAK cells

Reference	Number of Patients	Trial Results
[29]	6	No PR or SD No toxicity
[28]	9	1 CR, 2 PR Median survival: 53 wk
[32]	9	Neurologic side effects in all patients 1 PR
[33]	20	Median survival: 63 wk (36–201) Use of steroids did not influence in vitro generation of LAK or autologous stimulated lymphocytes
[46]	19	4 PR Median survival after therapy: 30 wk
[122]	5	No survival benefit
[123]	9	1 CR, 2 PR, 4 stable disease Median survival: 18 mo
[28]	19	1 CR, 2 PR Median survival after therapy: 53 wk
[45]	9	2 PR Median survival: 78 wk
[124]	28	1 CR, 2 PR (GBM) Median survival: 53 wk (GBM)
[34]	40	Median survival: 17.5 mo
[35]	33	Median survival: 20.5 mo

Abbreviations: CR, complete response; OS, overall survival; PR, partial response; SD, stable disease.

Five other clinical trials studied the use of CTLs from draining lymph nodes[39] or PBMCs after injection of ATCs.[39–43] In these trials, all CTLs were injected intravenously. Similar to those studies that injected CTLs intracerebrally, the results from these studies showed acceptable safety with minimal toxicity. Isolated toxicities included delayed-type hypersensitivity (DTH) to the vaccine[43] and fever and myalgias lasting 24 hours.[42]

The clinical benefits of these studies have been generally promising. These trials are summarized in **Table 3**. Despite each being only a phase I or pilot study with primary outcomes of safety and toxicity, all but one[40] of these trials reported partial responses or stable disease. Despite this finding, Holladay and colleagues[40] reported a time to recurrence of approximately 8 months, with 1 patient experiencing recurrence of GBM after more than 40 weeks and 7 patients experiencing recurrence after 8 or more months.

Table 3
Immunotherapy trials using CTLs

Reference	Number of Patients	Trial Results
[36]	5	2 PR 1 patient's survival reported at 104 wk
[125]	4	3 PR
[37]	10	1 CR, 4 PR Median survival: 5 mo
[38]	5	3 SD
[40]	15	No PR Time to recurrence >8 mo (n = 7)
[39]	10	3 PR, 1 SD Survival >1 y (n = 4)
[42]	10	3 PR
[41]	9	3 PR Survival >4 y (n = 2)
[43]	19	1 CR, 7 PR Median survival: 12 mo
[18]	6	1 CR, 2 PR

Abbreviations: CR, complete response; OS, overall survival; PR, partial response; SD, stable disease.

In the 10 trials using LAK cells or CTLs, 2 variables consistently reported as significant were the total number of cells infused and the use of corticosteroids during treatment. In these trials, the number of CTLs injected ranged between 3×10^7 and 10×10^{10}, with between 1 and 13 injections. Because the total number of CTLs as well as the method of delivery differed between studies, Kronik and colleagues[44] sought to define the optimum dose using a mathematical model that incorporated data from in vitro and in vivo studies, interactions with CTLs and major histocompatibility complex (MHC) receptors, and the effect of transforming growth factor β (TGF-β) and interferon γ (IFN-γ) on the antitumor immune response. These investigators reported the optimum calculated dose of CTLs as 27×10^9 total CTLs. As a result, they concluded that many immunotherapy trials may not have been successful because the dose given to patients was often inadequate (sometimes 20-fold smaller than that predicted to be effective).

The use of corticosteroids to control peritumoral edema was another factor that varied between

studies using LAKs or CTLs. Because of their immunosuppressive effect, corticosteroids were not used in 4 studies, suggesting that patients in these trials may have had a smaller tumor and potentially better outcomes compared with those patients who required steroid treatment.[29,34,35,45] Evidence for better survival when using LAK cells without the use of corticosteroids was reported by Dillman and colleagues[35] in their subset analyses. Other results point to the contrary, that corticosteroids did not have an effect on the number or functional activity of the infused effector cells.[31,33,46]

ACTIVE IMMUNOTHERAPY

Active immunotherapy involves administration of tumor antigens to prime the patient's endogenous immune system. Lysates of injected tumor antigens can be derived from irradiated tumor cells, nonspecific protein and mRNA lysates, and synthetic peptides. The delivery of these antigens is typically via vaccine, which often includes an immune adjuvant or the tumor antigen complexed to DCs, to increase the antitumor immune response. This strategy is considered advantageous because of the specificity afforded by directly injecting immunogenic tumor antigens and the long-term antitumor effect as a result of immunologic memory.

ATCs

ATCs have been studied in active immunotherapy strategies against HGG in 8 clinical trials and 2 case reports[47–54] for a total of 71 patients treated (**Table 4**). Of these studies, there was large heterogeneity in the number of cells infused, number of injections, and the use of immune adjuvants. The number of cells injected ranged from 10^6 to 10^{11} total cells per patient and they were given in 1 to 13 vaccinations. Only 2 of the 8 studies used immune adjuvants such as IL-2[48] and granulocyte-macrophage colony-stimulating factor (GM-CSF).[50] Although toxicities were minimal, 2 studies (n = 10 newly diagnosed GBM and n = 1 recurrent GBM), showed that no survival benefit was associated with treatment.[47,48]

Despite a large number of trials (n = 8), the available data do not show robust efficacy data despite most patients showing a strong immune response as assessed by ex vivo assays. Several studies reported a local skin reaction at the injection site.[48,50] Sobol and colleagues[47] reported an antitumor immune response mediated in part by CD8+ cytotoxic T cells, which were collected in the peripheral blood. Several groups reported significant increases of DTH reactions, numbers of tumor-reactive memory T cells, and numbers of CD8(+) TILs in recurrent tumors. Despite the presence of increased antitumor immune activity, most studies were unable to show a survival benefit in patients.

Table 4
Immunotherapy trials using ATCs

Reference	Number of Patients	Trial Results
47	1	No survival benefit
48	11	Median survival: 46 wk
49	12	2 CR, 4 PR
50	1	Survival: 10 mo
51	23	Median progression-free survival: 40 wk Median survival: 100 wk
52	3	Prolonged recurrence-free survival
53	12	1 CR, 1 PR, 2 minor response, 1 SD Median survival: 10.7 mo
54	5	3 SD

Abbreviations: CR, complete response; OS, overall survival; PR, partial response; SD, stable disease.

DCs

Glioma cells are poor APCs because of downregulation of costimulatory molecules[55] and the release of immunoinhibitory cytokines.[56–58] DCs are professional APCs that phagocytose foreign antigens and present them in the context of MHC to activate innate and adaptive immune cells. DC therapy is based on the concept that GBM cells are poor stimulants of the host's immune system and thus require DCs, acting as APCs, to internalize GBM antigens and present them to activate antitumor immune cells.[59] Nineteen studies have been published using DCs, with a total of 323 patients studied.[60–79] The cellular material complexed with APCs included whole ATCs, tumor lysate, tumor peptides, including the epidermal growth factor vIII (EGFRvIII), or tumor mRNA.

DC vaccinations are typically prepared using GM-CSF and IL-4 as adjuvants, although several groups have reported stimulating DCs with other cytokines.[62,64,68,70,77,80] These vaccines are typically injected intradermally or intranodally. Nishioka and colleagues[81] reported delivering DCs that expressed IL-12 directly to the tumor cavity and found that these cells were able to traffic to draining lymph nodes and activate cytotoxic, antitumor immune cells. Phase I studies have reported that

DC vaccines are safe and associated with only grade I and II vaccine site responses.

Results of these studies are summarized in **Table 5**. In brief, immunologic, radiologic, and clinical benefits were seen in roughly 40% of patients. A peripheral immune response, as measured by ex vivo assays or DTH reactions, was present in more than half of patients. Clinically, 13 studies reported efficacy in terms of beneficial survival compared with historical controls. Two studies did not find a correlation between peripheral immune response and survival.[71,78]

A subset of these clinical trials used vaccines containing DCs that present the EGFRvIII tumor antigen. The EGFRvIII receptor is the most common variant of the EGF receptor and is present on 27% to 67% of GBMs,[82,83] with its expression indicating a negative prognosis.[84] Furthermore, its expression is limited to GBM cells and is not expressed in normal brain. The first clinical trial using DCs loaded with EGFRvIII antigen against HGG was the Vaccine for Intra-Cranial Tumors I (VICTOR I, n = 16 patients). This phase I study used mature DCs loaded with 500 μg of DCs that were pulsed with PEPvIII, a protein that spans the EGFRvIII fusion junction, and conjugated to keyhole limpet hemocyanin (KLH). Vaccines were given 2 weeks after the completion of radiation therapy. After vaccination, all patients showed ex vivo immune responses without any serious clinical side effects. The results of this study were promising, with 2 of the 3 patients with grade III glioma alive without evidence of tumor progression at 66.2 and 123.7 months after vaccination. In vaccinated patients with GBM, the median time to progression (TTP) was 46.9 weeks, with the median survival reported as 110.8 weeks.[85]

The follow-up phase II trial, A Complementary Trial of an Immunotherapy Vaccine Against Tumor-Specific EGFRvIII (ACTIVATE) used DCs loaded with PEPvIII. Similar to the phase I trial, after vaccination, ex vivo assays showed increased titers of anti-EGFRvIII and anti-KLH antibodies and an increase in CD8+, IFN-γ–expressing, EGFRvIII-specific T cells. Clinically, the median TTP was 64.5 weeks and median survival reported as 126.1 weeks.

Although the ACTIVATE study was ongoing, TMZ was initiated as standard of care, along with surgery and radiation. The ACTIVATE II trial was then initiated (n = 21 patients) to determine the efficacy of EGFRvIII vaccine (CDX-110) in combination with TMZ. In this trial, the CDX-110 vaccine was administered on day 21 of the 28-day TMZ cycle, which resulted in similar anti-EGFRvIII immune activity as seen in the previous trials.

Table 5
Immunotherapy trials using DCs

Reference	Number of Patients	Trial Results
62	8	6 SD
67	9	Median survival: 455 d
64	10	2 minor responses, 4 SD
66	10	Median survival: 133 wk
70	15	4 PR, 2 SD
71	12	Median survival: 23.4 wk
73	13	1 CR, 3 PR Survival >18 mo (n = 3)
74	34	Median survival: 642 d Time to progression: 167 d
76	12	Time to progression: 6.8 mo Median survival: 22.8 mo
Others: 61,63,65,68,69,72,75,77,80,126,127		

Abbreviations: CR, complete response; OS, overall survival; PR, partial response; SD, stable disease.

IMMUNOMODULATION

One of the primary challenges in successful antitumor immune responses is the immunosuppressive milieu of the tumor microenvironment. The tumor microenvironment is a critical step in mediating antitumor immunity by the host immune system.

Cytokines

Of the multitude of immunosuppressive cytokines in the tumor microenvironment, a small number of cytokines have been targeted in clinical trials. TGF-β promotes immunosuppression in HGG by inhibiting T-cell activation and proliferation, blocking IL-2 production, suppressing activity of natural killer cells, and promoting T_{reg} activity.[86,87] Early phase I studies using trabedersen, a synthetic antisense phosphorothioate oligodeoxynucleotide that is complementary to the human TGFβ2 gene, showed that the drug was safe and associated with long-lasting remissions in some patients.[88] A phase IIb trial comparing trabedersen with standard chemotherapy in patients with recurrent HGG reported a median survival of 13.1 months with an 80-μM dose of trabedersen, 12.0 months with the 10-μM dose, and 11.0 months with standard chemotherapy. Overall survival at 12 months was not significantly different, although there was a trend toward increased survival in patients with grade III glioma receiving the 10-μM dose at 2 years.[89]

IL-2 is a proinflammatory cytokine that activates T cells and helps naive T cells differentiate along

the Th1 pathway.[90] Current trials using IL-2 are focused on local delivery because pharmacokinetic data show that high levels of systemically administered rIL-2 are needed to penetrate the CNS and are associated with prohibitive toxicities.[91] Early studies using IL-2 in combination with other immunotherapies including IFN-α[92] or LAK cells[32] reported high rates of neurologic side effects. When used in combination with IFN-α, patients experienced somnolence, headache, and increased peritumoral edema. When rIL-2 was used in combination with LAK cells, all patients had increases in cerebral edema. In another trial reported by Colombo and colleagues,[93] a total of 12 patients underwent gene therapy and received an intratumoral injection of retroviral IL-2 vector-producing cells (RVPCs). Results of this trial were promising in terms of safety because only grade I/II toxicities were noted. Biopsy samples after administration of the RVPCs showed an increase in Th1 cytokine levels. Progression-free survival and overall survival were reported as 47% and 58%, respectively, at 6 months and 14% and 25% at 1 year.

IFNs are secreted by immune cells in response to the presence of tumor cells and activate molecular pathways involved in coordinating an antitumor response against GBM. Three different IFNs have been tested in clinical trials; IFN-α, IFN-β, and IFN-γ.[94,95] Results of these studies are listed in **Table 6**.

Trials using IFN-α have produced mixed results in terms of both safety and efficacy. The first phase I study showed that treatment with IFN-α was safe and efficacious.[96] The follow-up phase II study of bis-chloroethyl-nitrosourea (BCNU) in combination with radiation and IFN-α resulted in a response rate of 29% in 35 patients with recurrent glioma. This phase II study also reported substantial constitutional side effects.[97] The phase III study of 214 patients with stable HGG involved randomization to BCNU or BCNU and IFN-α as a second course of treatment after they received surgery, radiation, and chemotherapy. Patients receiving IFN-α experienced fever, chills, myalgias, and neurocortical symptoms. Furthermore, there was no significant difference in TTP or overall survival.[98]

IFN-β has been tested in several trials, with mixed results. The first study evaluated escalating doses of IFN-β to 7 patients with recurrent glioma. The investigators reported that there was no radiographic response to the treatment, although stable disease was reported for 3 patients for a total of 8 to 26 weeks.[99] A phase I study in children with recurrent tumors (including glioma) tested a dose escalation of IFN-β, with the maximum tolerable dose reported as 500 mIU/m^2. Partial responses were seen in 4 patients (n = 2 high-grade astrocytoma, n = 2 brain stem glioma).[100] Fetell and colleagues[101] reported that a phase I study showed that infusion of

Table 6
Immunotherapy trials using immunomodulation

Reference	Number of Patients	Modulated Cytokine	Trial Results
88	24	TGF-β	3 CR, 7 SD Overall survival: 146.6 wk (anaplastic astrocytoma), 44 wk (GBM)
89	89	TGF-β	Median survival: 39.1 mo (10-μm dose) vs 35.2 mo (80-μm dose)
93	12	IL-2	4 minor response, 4 SD Progression-free survival at 6 mo (47%) and 12 mo (14%) Overall survival at 6 mo (58%) and 12 mo (25%)
96	15	IFN-α	Median survival: 44 mo
97	35	IFN-α	Median survival: 13.3 mo
98	275	IFN-α	No difference in TTP or overall survival
99	7	IFN-β	3 SD
100	21	IFN-β	4 PR
101	20	IFN-β	3 SD
94	28	IFN-γ	Median overall survival no different from historical controls
95	14	IFN-γ	No difference in survival from patients who did not receive IFN-γ
70	15	IL-12	4 SD, 1 mixed response

Abbreviations: CR, complete response; OS, overall survival; PR, partial response; SD, stable disease; TTP, time to progression.

IFN-β directly into the tumor cavity using Ommaya reservoir was well tolerated. Stable disease was reported in 3 patients, with the best response producing disease stability up to 539 days.

CHALLENGES

Challenges Presented by Tumor Biology

Three major challenges to immunotherapy presented by tumor biology include immune-editing, decreased antigen presentation by glioma cells, and decreased immune cell activation.

To eradicate a tumor, the immune system must be able to recognize a tumor-specific antigen, activate other immune cells, and then mount a substantial antitumor response. One major challenge presented to the immune system, and the use of immunotherapy as a treatment strategy, is the concept of immune-editing. Immune-editing consists of 3 phases: elimination, equilibrium, and escape. Elimination refers to the antitumor function of both the adaptive and innate immune system and is driven by the production of IFN-γ. Equilibrium is the period in which immune cells become latent to partially eradicated tumor. Escape is when the tumor escapes from immunosurveillance and becomes resistant to antitumor immune function, usually via genomic instability or downregulation of key antigens.[102] Immune-editing has been shown to exist in the treatment of HGG, especially in trials involving dendritic vaccines that target the EGFRvIII antigen. In the EGFRvIII vaccine trial reported by Sampson and colleagues,[76] 82% of patients with recurrent tumor had lost expression of EGFRvIII.

Another notable challenge is the presence of an immunosuppressive tumor microenvironment, causing decreased antigen recognition and depressed immune cell activation. Glioma cells show decreased HLA expression,[103] and in a recent study, Facoetti and colleagues[104] reported a loss of HLA-I expression in 50% of patients, with 80% of these patients showing a selective loss of HLA-A2. Macrophages and microglia also have a decreased potential for antigen presentation. In vitro data suggest monocytes lose phagocytic activity after exposure to glioma cells,[105] whereas in vivo data suggest that MHC class II activation is significantly depressed in microglia and macrophages isolated from glioma compared with normal brain.[106]

The other notable aspect of tumor-associated immunosuppression is depressed immune cell activation. CD4+ cells isolated from both tumor and peripheral blood show depressed function,[107,108] proliferative responses, and synthesis of IL-2 in patients with glioma.[109] Although increased CD8+ infiltrating lymphocytes have been shown in some studies to be associated with increased patient survival,[110–112] Hussain and Heimberger[15] reported that most tumor-infiltrating CD8+ cells are not activated.

The expression of immunosuppressive molecules and release of immunosuppressive cytokines are also associated with decreased immune cell activation. Increased expression of the surface molecules FAS, galectin-1, and B7-H1, which are all involved in regulating apoptosis, leading to subsequent decreases in tumor-infiltrating lymphocytes, have all been described.[113–116] Similarly, the release of cytokines such as IL-10,[117] prostaglandin E_2,[118,119] and TGF-β[120] are increased in the glioma microenvironment, leading to decreased immune cell activation.

Challenges Presented by Current Clinical Trials

Clinical trials for immunotherapy in HGG have mostly been small phase I or pilot studies in small cohorts of patients, leading to possible confounding prognostic variables. Although inclusion criteria usually require a histologic diagnosis of grade III/IV glioma, newer evidence suggests that a molecular classification of glioma may better subtype glioma tumors. This classification, reported by Verhaak and colleagues,[121] consists of classic, mesenchymal, proneural, and neural. Using a molecular diagnosis versus a histologic diagnosis as inclusion criteria for future clinical trials may lead to more uniform patient cohorts because differing responses to classic treatments are seen in patients with a molecular diagnosis. The investigators report a trend toward longer survival in the proneural subtype, despite poor responses to aggressive treatment protocols. Similarly, the same group report that the classic and mesenchymal subtypes showed a similar survival benefit; however, these tumors were susceptible to treatment.

Because of small patient cohorts typically seen in immunotherapy trials for HGG, dose escalation studies are rarely feasible, leading to a lack of a maximum tolerated dose. This heterogeneity in dose as well as the inability to reach a maximum tolerated dose may lead to results that may not reflect results seen at higher doses of vaccine.

SUMMARY

Despite several clinical trials evaluating immunotherapy as an adjuvant therapy for HGGs, robust efficacy for this treatment paradigm is lacking. Although nearly every clinical trial has reported induction of a peripheral immune response ex vivo, there was not a robust correlation between peripheral immune responses and patient survival.

One of the difficulties 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. Many intrinsic and extrinsic factors may influence trial results, including the use of other adjuvant agents that selectively deplete specific cell populations, patient selection, clinical trial design, and a wide variety of doses and methods of administration.

Despite these challenges, the cellular level specificity and surveillance against tumor cells are an appealing benefit to extending the survival of patients with HGG. Moving forward, well-designed clinical trials with standard doses and more homogenous patients will add stronger evidence for the use of immunotherapy as a standard adjuvant treatment of patients with HGG.

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