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Mini-review

Immunotherapy for glioma: Current management and future application

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ABSTRACT

Gliomas are intrinsic brain tumors that originate from neuroglial progenitor cells. Conventional therapies, including surgery, chemotherapy, and radiotherapy, have achieved limited improvements in the prognosis of glioma patients. Immunotherapy, a revolution in cancer treatment, has become a promising strategy with the ability to penetrate the blood-brain barrier since the pioneering discovery of lymphatics in the central nervous system. Here we detail the current management of gliomas and previous studies assessing different immunotherapies in gliomas, despite the fact that the associated clinical trials have not been completed yet. Moreover, several drugs that have undergone clinical trials are listed as novel strategies for future application; however, these clinical trials have indicated limited efficacy in glioma. Therefore, additional studies are warranted to evaluate novel therapeutic approaches in glioma treatment.

1. Introduction

Gliomas are the most common primary tumors in the brain, accounting for 81% of central nervous system (CNS) malignancies. They typically arise from glial or precursor cells and develop into astrocytoma, oligodendroglioma, ependymoma, or oligoastrocytoma [1,2]. According to the World Health Organization (WHO) classification, gliomas are categorized into four grades, among which grade 1 and grade 2 gliomas indicate low-grade ones, and grade 3 and grade 4 gliomas indicate high-grade glioma (HGG) [3]. Typically, a relatively high grade is related to a poor prognosis. The 10-year survival rate in low-grade glioma is 47% with a median survival time of 11.6 years [4]. For HGG, the median overall survival (OS) time of grade 3 glioma patients is approximately 3 years, whereas grade 4 glioma has a poor median OS time of 15 months [5]. Glioblastoma (GBM) is the most common type of grade 4 gliomas. Recently, it was found that glioma patients with mutations in isocitrate dehydrogenase (IDH) enjoys a relatively favorable survival [6,7]. In addition, O-6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation has been found to be a strong prognostic factor in patients with GBM [8].

Despite the fact that numerous cancer therapies have been developed over the past decades, few drugs have been approved by the Food and Drug Administration (FDA) in the treatment of glioma. One reason accounting for the lack of progress is the blood-brain barrier, which is composed of endothelial cells, capillaries and basement membranes. This unique structure in the CNS prevents the majority of antitumor drugs from entering the brain, bringing challenges in the development of antiglioma drugs [9,10].

Multiple studies have demonstrated the immunosuppressive nature of glioma, which regulates antitumor immune responses. Glioma cells express increased levels of immunosuppressive factors such as programmed cell death 1 ligand (PD-L1) and indolamine 2,3-dioxygenase (IDO), which limits the presentation of antigens [11,12]. Glioma-associated macrophages secrete interleukin (IL)-10 and transforming growth factor β (TGF-β), which decrease the activities of immune cells [13,14]. Moreover, regulatory T (Treg) cells in the glioma microenvironment mediate immunosuppressive effects by exhausting cytotoxic T lymphocytes, which could destroy tumor cells directly [15]. A better understanding of the immunosuppressive environment in glioma can help with the comprehension of the mechanism of immunotherapy.

Given that the 2018 Nobel Prize in Medicine was awarded to James Allison and Tasuku Honjo for their discovery of the cancer therapy approach involving the inhibition of negative immune regulation [16], immunotherapy currently holds a leading position in cancer care. To date, the conventional therapy for glioma consists of surgical resection, temozolomide (TMZ), and radiation, which is far from sufficient in combating cancer development [17]. In this review, we explicate the current management of glioma, describe multiple preclinical and

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clinical studies evaluating the efficacy of immunotherapies for glioma, and discuss further clinical studies that attempt to investigate novel strategies for glioma treatment.

2. Current management of gliomas

Today, the standard of care for gliomas includes maximal resection followed by concomitant radiotherapy and chemotherapy with TMZ within 30 days after surgery. The role of TMZ in glioma treatment was established in 2005, when a study showed that the combination of TMZ with radiotherapy significantly prolonged the median survival of GBM patients compared with radiotherapy alone [18].

In addition to TMZ, bevacizumab and tumor-treating fields (TTF) have been approved by the FDA for the treatment of glioblastoma. Bevacizumab is a synthetic monoclonal antibody targeting vascular endothelial growth factor (VEGF). A phase II clinical trial demonstrated the safety and antitumor activity of bevacizumab alone and bevacizumab combined with irinotecan in patients with recurrent glioblastoma [19]. The encouraging efficacy of bevacizumab impelled its formal approval by the FDA in the standard treatment for glioblastoma [20]. TTF is an electromagnetic field therapy that selectively damages proliferating cells by applying low-intensity, intermediate-frequency alternating electrical fields [21]. A prospective phase III clinical trial showed that a combination of TTF with TMZ significantly prolonged progression-free survival (PFS) and OS in GBM patients [22]. Considering the limited resources for glioma treatment, additional studies are required to investigate novel approaches combating with this malignancy.

Currently, novel immunotherapeutic strategies have been well studied in various preclinical and clinical studies. Dramatic responses have been detected during clinical trials, in which immune checkpoint inhibitors and CAR-T cells exhibit promising efficacy. Moreover, combination of different immunotherapies are worthy of exploration. Further studies are required to determine whether immunotherapy can be implemented as part of standard therapy for glioma.

3. Immune checkpoint blockade

Previous studies have shown that therapeutic inhibition of IDO, CTLA-4, or PD-L1 in glioma mouse models notably reduces tumor-infiltrating Treg cells numbers and significantly increases the long-term survival [23]. Immune checkpoint blockade appears to be a promising strategy in glioma immunotherapy [Fig. 1].

3.1. PD-L1

PD-L1 is an immune checkpoint molecule related to programmed cell death. Activation of PD-L1 suppresses the activity of T lymphocytes and mediates immune evasion by cancer cells [24]. The expression of PD-L1 has been detected in human glioma tissues and found to be related to glioma grade. These findings endorse the potential of PD-L1 as a target in cancer treatment [25]. In recent years, the application of immunotherapy targeting the PD-L1 axis has exhibited remarkable clinical efficacy in the treatment of melanoma and non-small cell lung cancer [26,27]. In a study using orthotopic glioma stem cell-like cell (GSC) mouse models to evaluate PD-1-inhibited natural killer (NK) cells, researchers found that the median survival time of the PD-1 inhibited NK cell group was prolonged to 44 days, while the survival time in the NK cell treatment group was 35 days and that in the control group was 29 days. This study indicated that the blockade of PD-1 could promote the cytotoxicity of NK cells against GSC [28]. The combination of PD-1 inhibitors with other therapeutic approaches is another attractive option. In a GL261 cell implanted mouse model, the combination of anti-PD-1 immunotherapy and stereotactic radiosurgery prolonged the median survival to 52 days compared with 27 days achieved with radiotherapy-alone and 30 days achieved with anti-PD-1-immunotherapy alone [29]. Moreover, the combination of an anti-TIM-1 antibody, anti-PD-1 immunotherapy, and SRS significantly increased the OS of a GBM mouse model compared with other treatments [30]. Additionally, the combination of a PD-1 inhibitor and VEGF inhibitor was found to be tolerable and promising in animal models and clinical trials [31,32]. Furthermore, triple-combination immunotherapy with an anti-PD-1 monoclonal antibody, GVAX, and an anti-OX40 monoclonal antibody is highly effective against murine intracranial gliomas [33].

Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody that has been approved by the FDA as a first-line treatment for unresectable or metastatic melanoma in combination with ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) monoclonal antibody. The safety and effectiveness of nivolumab and ipilimumab in recurrent glioblastoma have been assessed in a phase III clinical trial (NCT02017717). The results showed that the combination of nivolumab and ipilimumab does not improve overall survival. Nivolumab monotherapy was best tolerated and achieved a better median OS compared with a combined regimen (10.4 months vs 9.2 months) [34]. A single-arm phase II clinical trial tested the effectiveness of neoadjuvant nivolumab in patients with glioblastoma, and the results showed that neoadjuvant nivolumab induced a local immunomodulatory treatment effect [35]. Pembrolizumab is a humanized monoclonal antibody against PD-1 with robust clinical activity and acceptable safety [36]. Recently a randomized, multicenter clinical trial evaluated the immune response and survival following neoadjuvant pembrolizumab administration to patients with glioblastoma. The findings suggested that the application of neoadjuvant pembrolizumab enhanced both local and systemic immune responses against tumors. Patients receiving adjuvant pembrolizumab alone had a median OS time of 228.5 days, whereas the median OS time in neoadjuvant group was 417 days [37].

The antitumor activity of anti-PD-1 immunotherapy has been well studied in mouse models, and its combination with other immunotherapy provides novel approaches for the treatment of glioma. Moreover, the practical application of anti-PD-1 immunotherapy has been well assessed in clinical trials [Table 1]. To date, 33 studies have been registered at ClinicalTrials.gov. We believe that anti-PD-1 immunotherapy is a promising therapeutic approach against glioma.

3.2. CTLA-4

CTLA-4, also known as CD152, is a protein receptor that binds to B7 and blocks immune responses [38]. The ligands of CTLA-4 are CD86 and CD80, which are also the ligands of the costimulatory receptor CD28. Since CTLA-4 has higher affinities for both ligands than does CD28, it competitively inhibits the activation of CD28, leading to the suppression of T-cell activity [39]. A previous study showed that glioma patients had elevated CTLA-4 expression [40], and the expression is correlated with the progression of gliomas [41]. The administration of an anti-CTLA-4 monoclonal antibody reduces the level of CD4 + FoxP3 + Treg cells, leading to the eradication of glioma and improved long-term survival in mouse models [42,43]. This result was also confirmed by another study using a combination of IL-12 and an anti-CTLA-4 antibody [44]. Moreover, the combination of anti-CTLA-4 and anti-PD-1 antibodies has been shown to cure 75% of murine glioblastoma compared with 50% and 15% for single-agent anti-PD-1 and anti-CTLA-4 antibodies, respectively [45]. A triple therapy regimen of agonistic anti-4-1BB antibodies, anti-CTLA-4 antibodies, and focal radiotherapy results in an increased density of tumor-infiltrating lymphocytes, with at least a 50% increase in tumor-free survival [46]. Notably, all the studies listed above built glioma mouse models using GL261 cells. However, a recent study revealed that an SB28 mouse model was a much more suitable model to investigate glioblastoma immunotherapy than the GL261 mouse model, with lower MHC-1 expression and modest $CD8^+$ T cell infiltration [47].

In regard to the practical application of anti-CTLA-4

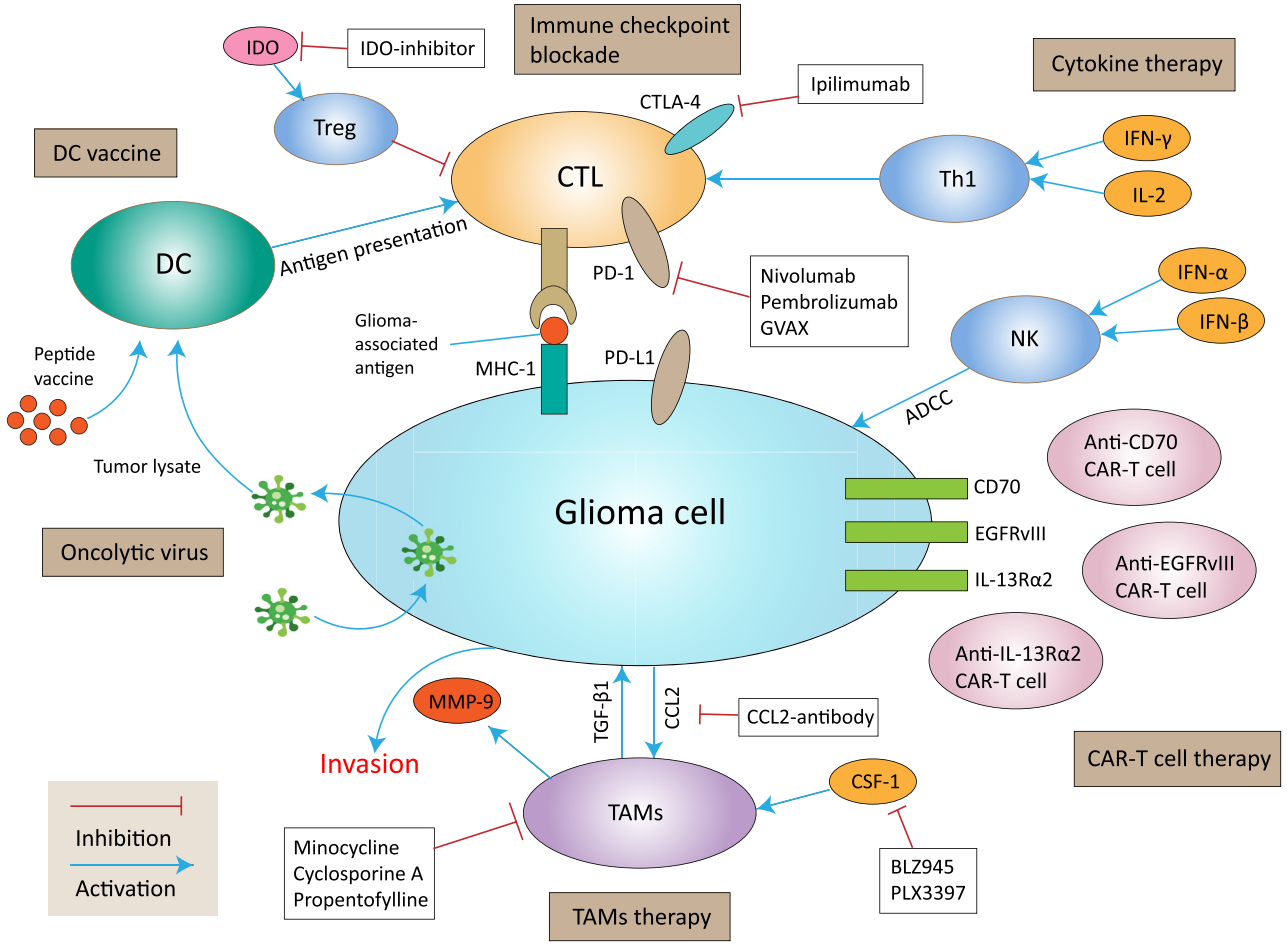

Fig. 1. Current strategies for immunotherapy in glioma. Oncolytic viruses can destroy glioma cells and release new viruses to help destroy the remaining tumor. The released tumor lysate can be recognized by DCs, which are commonly used in DC vaccines. DCs are efficacious in antigen presentation and can induce the activation of CTLs, which subsequently kill glioma cells. Glioma cells often escape immune surveillance by activating immune checkpoint ligands such as PD-1, CTLA-4, and IDO. The inhibition of PD-1, CTLA-4, and IDO can effectively prevent this interaction. Cytokines such as IFN-γ and IL-2 can activate Th1 cells, which stimulate the antitumor activity of CTLs. IFN-α and IFN-β can activate NK cells, which destroy tumor cells via ADCC. Glioma-associated antigens, including IL-13Rα2, EGFRvIII, and CD70, are present on the surfaces of tumor cells, which can be recognized by CTLs with the promotion of MHC-1 expression. These tumor-associated antigens are being exploited as targets of genetically modified CAR-T cells. Tumor-associated macrophages activated by CSF-1 and CCL2 can secrete MMP-9 and TGF-β1, facilitating the invasion of glioma cells. Inhibiting these interactions can reduce the invasion of glioma cells.

immunotherapy, the safety and tolerability of ipilimumab combined with other drugs such as nivolumab, temozolomide, or radiation therapy are under evaluation in multiple phase I and phase II clinical trials. Moreover, an undergoing clinical trial was designed to assess the immunologic changes that occur in glioblastoma treated with tremelimumab, another anti-CTLA-4 IgG2 monoclonal antibody, and

Table 1
Selected ongoing clinical trials of PD-1/PD-L1 antibodies in glioma.

Antibody	Study Number	Intervention	Disease	Phase	Primary Outcome Measures	Status
Nivolumab	NCT03925246	Nivolumab	IDHmut HGG	2	24 weeks PFS	Recruiting
Nivolumab	NCT03557359	Nivolumab	IDHmut Gliomas	2	ORR	Recruiting
Nivolumab	NCT03718767	Nivolumab	Glioma	2	6 months PFS	Recruiting
Nivolumab	NCT02335918	Varlilumab + Nivolumab	Glioma and other malignancies	1,2	TRAE, 12 months OS in GBM	Completed
Nivolumab	NCT03743662	Nivolumab + Radiation + Bevacizumab	MGMT Methylated GBM	2	OS	Recruiting
Nivolumab	NCT03173950	Nivolumab	CNS Cancers	2	PFS, ORR	Recruiting
Pembrolizumab	NCT02311582	Pembrolizumab + MRI-guided Laser	Malignant Glioma	1,2	MTD, PFS	Recruiting
Pembrolizumab	NCT04013672	Pembrolizumab + SurVaxM	Recurrent GBM	2	PFS	Not yet recruiting
Pembrolizumab	NCT02798406	Pembrolizumab + DNX-2401	GBM and gliosarcoma	2	ORR	Active, not recruiting
Pembrolizumab	NCT03899857	Pembrolizumab	GBM	2	12 months OS	Not yet recruiting
Pembrolizumab	NCT03797326	Pembrolizumab + Lenvatinib	Glioma and other malignancies	2	ORR, AE percentage, withdrawn percentage	Recruiting

* Clinical trials listed above have excluded those status being "unknown" and "terminated".
TMZ: Temozolomide; IDH: Isocitrate dehydrogenase; GBM: Glioblastoma; HGG: High-grade glioma; TRAE: treatment-related adverse event; PFS: progression free survival; OS: overall survival; MTD: maximal tolerated dose; ORR: objective response rate; AE: adverse event.

durvalumab as single agents and in combination (NCT02794883).

3.3. IDO

Indoleamine 2,3-dioxygenase (IDO) is an inducible, rate-limiting enzyme in tryptophan catabolism, with the immunomodulatory function of reducing the activity of T cells [48]. Emerging evidence indicates that the activation of IDO is involved in cancer development by helping tumor cells escape immune surveillance [49]. Recently, a systematic review and meta-analysis revealed that high expression of IDO1 was associated with poor prognosis in various types of cancer including gliomas [50]. A previous study showed that IDO inhibition combined with chemoradiation therapy prolonged survival in mice with glioblastoma. The inhibition of IDO allowed the chemoradiation to trigger an increased amount of complement C3 at tumor sites, leading to immune-mediated tumor destruction [51]. Temozolomide is an alkylating agent currently used as the first-line treatment for glioblastoma. The combination of temozolomide and an IDO inhibitor was proven to increase survival and reduce tumor growth in mice with glioblastoma [52]. Moreover, this antitumor activity may stem from the promotion of $CD3^+$, $CD4^+$, and $CD8^+$ T cells, which suppress the proliferation of tumor cells [53].

IDO inhibitors seem to have promising efficacy in preclinical studies. However, the negative results of a phase III trial in melanoma patients revealed no improvements in PFS or OS for an IDO inhibitor compared to monotherapy with pembrolizumab, indicating that IDO is not an appropriate target in the majority of melanoma patients [54]. Other IDO inhibitors such as indoximod do not show promising efficacy in clinical cancer treatment [55]. Therefore, further studies are needed to explore a novel strategy using IDO inhibitors for cancer treatment.

4. Cytokine therapy

Cytokines are produced by the immune system and can modulate immune responses. They are often employed by tumors as protective mediators to reduce the immune response; however, these immunoregulatory effects can also be applied to induce immune responses targeting tumor cells [56] [Fig. 1]. The most commonly used cytokines in cancer therapy are interleukins and interferons.

Interleukins such as IL-2, IL-4, and IL-13 have a multitude of immune effects. IL-2 is a growth factor necessary for the activation of T cells. IL-2 has been approved by the FDA to treat renal cell carcinoma and melanoma [57]. The safety of IL-2 in patients with glioma was evaluated in 1986 [58]; however, considerable therapy-related side effects arise when the combination of systemic IL-2 and autologous tumor vaccination is administered [59]. The administration of combined therapy of herpes simplex virus type 1 thymidine kinase (HSV-TK) genes and IL-2-encoding genes to patients with recurrent GBM shows that the treatment is well tolerated and tumor responses are detected in 50% of patients [60]. IL-4 is a glycoprotein that can promote the growth and differentiation of helper T cells and cytotoxic T lymphocytes. In a phase I clinical study, adult patients with HGG received two vaccinations with autologous fibroblasts retrovirally transduced with HSV-TK genes and IL-4-encoding genes and mixed with irradiated autologous glioma cells, which induced significant clinical responses [61]. Another phase I clinical study evaluated the safety of a chimeric recombinant protein composed of IL-4 and *Pseudomonas* exotoxin (IL-4-PE) in 31 patients with recurrent HGG. Limited adverse effects were detected, but no deaths were attributed to the therapy [62]. IL-13 is derived from Th2 cells and shares a common receptor with IL-4. A phase I study confirmed the safety of a recombinant protein composed of IL-13 and *Pseudomonas aeruginosa* exotoxin A, termed IL-13-PE38QQR, in patients with recurrent HGG [63]. Futhermore, a phase III study showed that PFS of patients was prolonged (17.7 weeks vs 11.4 weeks) after treatment with IL-13-PE38QQR, but no significant difference in OS was detected between two patient groups [64].

Interferons (IFNs) are mainly classified into three groups: type I (IFN-α and IFN-β), type II (IFN-γ), and type III (IFN-λ). IFN-α has been approved for use in hematological malignancies such as leukemia and lymphomas and solid tumors such as melanoma and Kaposi sarcoma [56,65]. IFN-γ is effective against bladder carcinoma recurrence [66] and produces benefits in patients with ovarian carcinoma with acceptable toxicity [67]. For IFN-λ, its antitumor activity has mainly been exhibited in preclinical studies [68]. Two phase II trials showed that IFN-α improved the efficacy of TMZ in recurrent GBM patients compared to that in historical controls [69]. Moreover, IFN-β could enhance chemosensitivity to TMZ by reducing MGMT transcription in preclinical studies [70,71]. Furthermore, a phase I clinical trial showed that the addition of IFN-β to standard chemoradiotherapy with TMZ was well tolerated and might prolong the survival of patients with GBM [72]. Nagoya University conducted a multicenter clinical trial delivering an IFN-β-encoding gene via cationic liposomes to treat patients with HGG. The results showed that two of five patients achieved a more than 50% reduction in tumor size and that median survival was longer in the treated patients than in historical controls [73]. The combination of IFN-γ and radiotherapy or chemoradiotherapy shows no meaningful efficacy in cases of GBM or pediatric HGG [74,75].

Although the abovementioned studies did not reach conclusions regarding the efficacy of IL-2 and IL-4, these two treatment strategies are thought to be safe and have acceptable toxicity profiles. Further studies are needed to establish proof of IL-2 and IL-4 efficacy in cases of HGG. IL-13-based targeted toxins can potentially be used as an adjuvant therapy for HGG, but their application certainly requires further clinical studies. The combination of IFN-α or IFN-β with TMZ exhibits promising efficacy in patients with HGG, whereas the roles of IFN-γ and IFN-λ in the clinical treatment of glioma require further evaluation. However, the results of currently available preclinical studies suggest that IFN-γ and IFN-λ have potential as promising adjuncts in other therapeutic approaches.

5. Dendritic cell vaccines

Dendritic cell vaccines (DCVs) are vaccines composed of efficacious antigen-presenting cells (APCs) capable of provoking immune responses [Fig. 1]. DCs are generated in vitro using $CD14^+$ monocytes cultured with granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4 to differentiate immature DCs. Then, the DCs are loaded with tumor antigen and later injected back into the patient [76]. Currently, only one DCV, sipuleucel-T (Dendreon), has been approved by the FDA, and it was approved in 2010 for the treatment of metastatic prostate cancer [77].

In clinical studies of DCVs, most researchers have chosen autologous tumor lysate or cultured tumor cells from surgical specimens as the antigen, but some have chosen irradiated autologous tumor cells, tumor RNA from a surgical sample, or tumor-associated peptides [78]. Two phase I clinical trials were conducted to evaluate the safety of DCVs in patients with HGG. The results showed that a DCV using autologous glioma cells as the antigen was safe and feasible in patients with HGG [79,80]. Immune and clinical responses to a DCV in GBM were reported in a phase II clinical study, where 17 of 34 patients achieved a significant increase in median survival (642 days vs 430 days) [81]. In 45 children with a variety of central nervous system tumors, including 32 HGGs, a DCV was administered using tumor lysate as the antigen. The results showed that the HGG patients had a median survival time of 13.5 months, and 4 of 22 patients with GBM survived for greater than 24 months [82]. Furthermore, this DCV was used in patients with newly diagnosed GBM, whose median PFS time was 18 months with 3 patients surviving for more than 34 months [83]. However, another study found no benefit in patients with newly diagnosed GBM treated with a tumor lysate DCV [61]. No significant increase in survival was also the result of a phase II clinical study using tumor lysate DCV in patients with recurrent GBM [84]. A study using irradiated tumor cells as the DCV

antigen was conducted, however, only 4 of 11 patients with HGG experienced partial responses and 1 patient obtained a complete response [85]. Moreover, the promising efficacy of a DCV using a peptide specific for epidermal growth factor receptor variant III (EGFRvIII) conjugated to keyhole limpet hemocyanin as the antigen was detected in a phase I clinical study. The median OS time was 22.8 months in adults with newly diagnosed GBM [86]. In recent years, two phase II clinical trials using DCV have achieved impressive outcomes. One was conducted in 2011 by Chang et al. in 19 patients with HGGs using a DCV activated by irradiated tumor cells. The median survival time was 520 days and 18.8% of the patients survived for more than 5 years [87]. Another study was reported in the same year, 18 patients with newly diagnosed GBM received an adjuvant DCV, and 16 patients underwent conventional treatment only. The results showed a dramatic increase in OS in the DCV group compared with the control group (31.9 months vs 15.0 months) [88]. In addition, MGMT promoter methylation was found to be associated with improved OS. The OS of patients with methylated MGMT promoter was significantly higher than that of patients with unmethylated MGMT promoter [89,90].

The safety and efficacy of DCVs using tumor-associated antigens as target peptides have also been evaluated. A clinical study using a DCV primed with IL-13Rα2, EphA2, gp100, and YKL-40 as the antigens in patients with recurrent HGG showed a poor prognosis in vaccine-treated patients [91]. Similar results were detected in another study using WT-1, HER2, MAGE-A3, MAGE-A1, and gp100 as the primed antigens. However, a phase I trial using HER2, TRP-2, gp100, MAGE-1, IL-13Rα2, and AIM-2 as the DCV antigens showed promising efficacy, with median PFS and OS times of 16.9 months and 38.4 months, respectively [92]. Later in 2019, the same DCV, termed ICT-107, exhibited potent antitumor activity in a randomized phase II trial. Eighty-one patients receiving ICT-107 had significant improvements in median PFS compared with control-treated patients (11.2 months vs 9 months, respectively). HLA-A2+ patients showed elevated clinical and immune responses. Median OS was not significantly different between the two groups was not statistically significant, as only patients with methylated HLA-A1 had an OS benefit [93].

Other studies using transfected mRNA have been conducted. Seven patients with GBM treated with a DCV primed against transfected tumor mRNA had a median OS time of 759 days, while historical control had a median OS time of 585 days [94]. Another study used a pp65-transfected DCV mixed with GM-CSF and dose-intensified TMZ to treat patients with newly diagnosed GBM. Eleven patients had a median OS time of 41.1 months compared to that of 19.2 months for historical controls [95].

With various antigens as primers for DCVs, a phase I study was conducted to compare the safety, toxicity, and feasibility of two DCV-priming strategies: an autologous tumor lysate (ATL) and a glioma-associated antigen (GAA). Twenty-eight patients were enrolled in the ATL group and 6 patients were enrolled in the GAA group. Of note, the 6 patients in the GAA group were selected based on their human leukocyte antigen (HLA) type, which was deemed a limitation of this approach. The incidence, frequency, and severity of adverse events was similar between the two groups. The median OS time in the ATL group was 34.4 months, while that in the GAA group was 14.5 months. Interestingly, elevated frequencies of activated natural killer cells were detected in the GAA group and associated with shortened patient survival. Moreover, a decreased level of regulatory T lymphocytes was also associated with prolonged survival [96].

Relative safety and promising efficacy have been seen using DCV in the treatment of glioma. Currently, two phase II trials are registered at ClinicalTrials.gov. One study that was still enrolling is using a DCV primed with tumor samples, allogeneic hematopoietic stem cells, and cytotoxic lymphocytes as a first-line therapy in patients with GBM (NCT01759810). The other study that is currently recruiting is employing an mRNA-transfected DCV and comparing that treatment with adjuvant TMZ in patients with GBM (NCT03548571). Evaluation in large phase III clinical trials will definitely answer the question of whether DCVs are a feasible and potent therapeutic approach for patients with HGG.

6. Viral therapy

Oncolytic viruses are a form of immunotherapy that uses viruses to infect and destroy cancer cells. As infected cancer cells are destroyed by oncolysis, they release new infectious virus particles to help destroy the remaining tumor [Fig. 1]. In 2005, an oncolytic adenovirus, termed H101, was approved for the treatment of head and neck cancer in China [97]. In 2015, a genetically modified herpes simple virus (HSV), talimogene laherparepvec (T-VEC), was approved by the FDA for the treatment of metastatic melanoma [98]. Other oncolytic viruses such as retroviruses, measles viruses, and polioviruses exhibit promising antitumor activities in cancer treatment [99].

Adenoviruses have been extensively studied due to their prevalence and easy manipulation. Ad5-Δ24RGD, also called DNX-2401, is an oncolytic adenovirus that carries a 24-bp deletion in the transforming protein E1A and an insertion of an Arg–Gly–Asp (RGD) motif into the fiber knob. The combination of Ad5-Δ24RGD and radiotherapy achieves promising efficacy in mice with malignant glioma [100]. A phase I clinical study showed that intratumor injection of DNX-2401 resulted in long-term survival as well as dramatic responses, which were probably due to immune responses targeting tumor lysates [101]. In addition, a phase I study showed no significant safety issues or virus toxicity in an 8-year-old patient with diffuse intrinsic pontine glioma [102], but long-term follow-up studies are still required (NCT03178032). The combination of DNX-2401 with pembrolizumab (NCT02798406), IFN-γ (NCT02197169), or TMZ (NCT01956734) was under investigation. Another oncolytic adenovirus, ONYX-015, was designed with an attenuated E1B protein and can only replicate in p53-deficient tumor cells [103]. The maximum tolerated dose of ONYX-015 has not been defined; however, high safety was related to poor efficacy in patients with malignant glioma [104].

The use of oncolytic viruses derived from HSV strains is another promising approach for glioma therapy. R-115 is an oncolytic HSV retargeted to human erbB-2, and its combination with IL-12 results in 30% of animals achieving complete tumor eradication and induces a significant improvement in median OS in mice, warranting further clinical evaluation [105]. Another oncolytic HSV, G207, has been confirmed to be tolerable in combination with radiotherapy in patients with malignant glioma. G207 is administered intratumorally and results in the mean survival of 7.5 months [106]. The safety and effectiveness of G207 in both pediatric and adult patients with glioma are under evaluation in two clinical trials (NCT00028158 and NCT03911388). A second-generation oncolytic HSV, M032, can cause the tumor cells to secrete IL-12 before it is eliminated, which increases the antitumor effect of this therapy. The safety and tolerability of M032 are under evaluation in patients with GBM (NCT02062827).

The recombinant oncolytic poliovirus PVSRIPO recognizes the poliovirus receptor CD155, which is highly expressed in solid tumors. Intratumoral infusion of PVSRIPO exhibits promising efficacy as patients with GBM achieve 21% OS at 24 months and 36 months compared with historical controls, who achieved a 24 month survival rate of 14% and a 36 month survival rate of 4% [107].

Various studies have confirmed the safety and efficacy of oncolytic viruses for the treatment of glioma. However, large-scale studies are required to determine whether oncolytic viruses can be used as a standard therapy in glioma.

7. TAM therapy

Tumor-associated macrophages (TAMs) are usually defined as macrophages populating the tumor-surrounding microenvironment to promote tumor progression [108,109] [Fig. 1]. Previous studies have

suggested that TAM infiltration in gliomas is dominated by immunosuppressive M2 macrophages, which leads to an immunosuppressive tumor microenvironment and facilitates the progression of gliomas [110]. Microglia are yolk sac-derived myeloid cells that represent a major component of the innate immune system in the central nervous system [111]. Similar to macrophages, microglia are capable of polarization into the pro-inflammatory M1 subtype or the immunosuppressive M2 subtype [112]. Several studies have confirmed larger numbers of TAMs in higher-grade gliomas compared with lower-grade tumors using immunohistochemical staining [113,114]. The expression of macrophage genes is associated with tumor pathology, response to treatment, and OS in glioma patients [115]. After activation, microglia secrete TGF-β1, which promotes glioma invasion. Additionally, TGF-β1 expression was elevated when researchers co-cultured microglia and glioma cells [116]. This result was confirmed in another study, which suggested that the enhanced invasive capacity induced by TGF-β1 was more likely to occur in CD133+ glioma cells than in CD133-cells. Moreover, matrix metalloprotease 9 (MMP-9) plays a crucial role in promoting invasion of glioma cells [117]. In U87 glioma cells cocultured with microglia, the expression of CCL2 is significantly increased, which enhances the invasion of glioma cells with a high level of IL-6 in the coculture medium [118]. A study showed that the administration of an anti-CCL-2 antibody to mice bearing gliomas significantly inhibited the infiltration of microglia. Moreover, the combination of an anti-CCL2 antibody with temozolomide notably prolonged OS in glioma-bearing mice [119].

As TAMs depend on colony-stimulating factor (CSF) for differentiation and survival, BLZ945, a CSF-1 inhibitor, has been used to target TAMs in mouse glioblastoma models. The results showed that the inhibition of CSF-1 could decrease the M2 macrophage frequency in the TAM populations, leading to increased survival and tumor regression [120]. However, these therapeutic effects have not been seen in recurrent glioblastoma. The combination of a PI3K or IGF-1 inhibitor with a CSF-1 inhibitor in recurrent tumors significantly prolongs OS, providing a novel solution to CSF-1 inhibitor resistance [121]. PLX3397 is a CSF-1 inhibitor that can cross the blood-brain barrier in live animals. It can reduce the number of tumor-associated microglia and alleviate tumor invasion in glioblastoma mouse models [122]. A phase II clinical study evaluated the safety and effectiveness of PLX3397 in 37 patients with recurrent glioblastoma. The results showed that PLX3397 was well tolerated but did not produce a therapeutic effect, which warrants further studies to test the efficacy of combined strategies [123]. The antibiotic minocycline is a lipophilic molecule that attenuates the expression of microglial MMPs, exhibiting the potential to suppress glioma invasion [124]. Moreover, minocycline can be safely combined with radiation and bevacizumab in patients with recurrent gliomas [125]. In addition, the administration of cyclosporine A has been shown to reduce glioma proliferation and angiogenesis by inhibiting the infiltration of microglia [126]. Similar effects have been detected when propentofylline is used for glioma treatment [127].

Emerging evidence has shown that TAMs contribute significantly to the formation and maintenance of immunosuppression and tumor cell migration. TAMs also promote angiogenesis in glioma [128]. It seems that immunotherapy targeting TAMs has certain potential in glioma treatment. To date, the TAM inhibition strategy has only been evaluated in mouse models and in small clinical trials [Table 2], with no approval from the FDA yet. Additional studies are warranted to better understanding of the correlation between gliomas and TAMs to provide practical strategies for clinical application.

8. CAR-T therapy

Chimeric antigen receptors (CARs) are genetically synthetic immunoglobulin T cell receptor molecules that can recognize specific antigens and activate T cells [129] [Fig. 1]. CARs typically consist of an ectodomain and an endodomain, which are connected by a spacer region and transmembrane domain. The ectodomain recognizes a tumor-associated antigen expressed on the surface of cancer cells in cancer therapy. The endodomain contains an intracellular T-cell signaling domain derived from CD3 and costimulatory molecules such as CD28, OX40, CD137, and CD27 [130]. After an antigen is bound to the ectodomain, an activation signal is transmitted by the CD3 domain and the signal is perpetuated by the costimulatory molecule domains [131].

In 2017, the FDA approved two CAR-T cells therapies for B-cell lineage acute lymphoblastic leukemia and diffuse large B-cell lymphoma that act by targeting the CD19 antigen, a biomarker of B cells. Since CAR-T cell therapy opened the door to a new era of cancer treatment, multiple CARs have been developed to target glioma, including CARs targeting IL13Rα2, EGFRvIII, HER2 and CD70 [132]. A previous study showed that intracranial delivery of first-generation IL13Rα2 CAR-T cells in patients with glioblastoma was well tolerated with promising antitumor activity [133]. This therapeutic strategy was evaluated by a phase I clinical trial, in which complete remission was detected in a single patient according to the report [134]. Second-generation IL13Rα2 CAR-T cells include a CD137 costimulatory domain, and an artificial platform has been used to enrich for central memory T cells. The antitumor efficacy and persistence of these CAR-T cells are elevated compared with those of first-generation IL13Rα2 CAR-T cells in glioblastoma mouse models [135]. In an orthotopic murine glioblastoma xenograft model, infusion of HER2 CAR-T cells leads to T cell proliferation and IFN-γ and IL-2 secretion, mediating the regression of HER2-positive glioblastoma [136]. The safety and feasibility of HER2 CAR-T cells were assessed in phase I clinical trial. The results showed that the HER2 CAR-T cells were well tolerated and exhibited clinical benefit in patients with glioblastoma [137]. During CAR-T cell therapy, antigen escape variants can lead to tumor recurrence after treatment. However, tandem CAR-T cells, including those targeting HER2 and IL13Rα2, can diminish antigen escape, increase antitumor efficacy, and improve survival in glioblastoma mouse models [138]. Moreover, intracerebral EGFRvIII CAR-T cell infusion can inhibit tumor growth via IFN-γ secretion in murine glioblastoma models [139,140]. This antitumor activity requires lymphodepleting host conditioning, and it can be inhibited by a short peptide that binds to the epitope expressed on target cells [141]. Furthermore, the EGFRvIII CAR-contained ICOS signaling domain also exhibits efficient antitumor activity against EGFRvIII expressing gliomas [142]. Similar antitumor activity mediated by EGFR inhibition was also detected in a clinical trial using nimotuzumab [143]. In addition, CD70 was detected as a novel immunosuppressive ligand in IDH wild-type LGGs and in glioblastoma in a study. The study also showed that the expression of CD70 was associated with poor survival and that CD70 CAR-T cells could specifically regress $CD70^{+}$ glioblastoma in xenograft models, furnishing a novel CAR target for glioma immunotherapy [144].

Currently, 26 clinical trials using CAR-T cells in the treatment of glioma have been registered [Table 3]. Most of these CAR-T cells target EGFR, HER2, or IL13Rα2, but some novel targets such as GD2, EphA2, MUC1, and CD147, are also included. The safety and antitumor activity of these CAR-T cells have been evaluated in the above studies. The utilization of CAR-T cells can precisely target tumor cells, thus not only increasing the efficacy but also reducing concurrent toxicity. However, the efficacy of CAR-T cell therapy remains moderate because of heterogeneous antigen expression and limited T cell function in the tumor site. Novel strategies have been developed to ameliorate CAR-T cell function such as transgenic expression of pro-T-cell activity cytokines [145] and genetic approaches to avoid checkpoint blockade [146].

9. Future application

Great efforts have been made to investigate novel agents against glioma. In 2019, a novel CAR-T cell product targeting B7-H3, a member of the B7/CD28 family, exhibited potent antitumor activity against solid tumors such as lung cancer, prostate cancer, breast cancer and

Table 2
Ongoing clinical trials of TAMs therapy in glioma.

Drug	Study Number	Intervention	Disease	Phase	Primary Outcome Measures	Status
PLX3397	NCT01349036	PLX3397	Recurrent GBM	2	Response rate, plasma parameters	Terminated
PLX3397	NCT01790503	PLX3397 + TMZ + radiation	Newly diagnosed GBM	1, 2	PFS	Active, not recruiting
minocycline	NCT01580969	minocycline + bevacizumab + radiation	Recurrent Glioma	1, 2	Adverse event	Completed
minocycline	NCT02770378	Minocycline + TMZ vs other drugs + TMZ	GBM	1, 2	Dose-limiting toxicity, Objective stable disease	Active, not recruiting
minocycline	NCT02272270	Minocycline + TMZ + radiation	HGG	1	Safety and tolerability	Completed
cyclosporine	NCT00003625	Cyclosporine or Etoposide or Vincristine sulfate + Radiation	Brain tumors	1	Event Free Survival	Completed

TMZ: Temozolomide; GBM: Glioblastoma; PFS: Progression free survival; HGG: High-grade glioma.

melanoma in mouse models [147,148]. In addition, preclinical studies have demonstrated the antitumor activity of B7-H3 CAR-T cells in GBM as well as pediatric malignancies [149,150]. These promising results pave the way for further clinical studies using B7-H3 CAR-T cells for the treatment of GBM (NCT04077866) and pediatric gliomas (NCT04185038).

Fcγ CR-T cells also play a crucial role in CAR-T cell therapy. Similar to traditional CAR-T cells, Fcγ CR-T cells have a common intracellular tail as the stimulatory factors. In contrast, the extracellular CAR single-chain variable fragment is replaced with the Fcγ receptor (FcγR), which is also called CD16. FcγR can combine multiple monoclonal antibodies targeting various tumor-associated antigens (TAAs) [151] and stimulate NK cells to identify and destroy tumor cells through antibody-dependent cellular cytotoxicity (ADCC) [152]. Therefore, Fcγ CR-T cells can serve as a novel immunotherapy in cancer treatment. However, no study has demonstrated the antitumor activity of Fcγ CR-T cells in glioma, which indicates the need for additional explorations.

Bispecific antibodies (BsAbs) are attracting much attention as an immunotherapy strategy. BsAbs can redirect killer cells to tumor cells in an MHC-independent way and block two oncogenic biomarkers simultaneously [153]. T cells armed with an anti-CD3 × anti-EGFR BsAb can target tumor cells precisely, leading to tumor regression and prolonged survival in glioma mouse models [154,155]. Since M2 macrophages in the tumor microenvironment promote tumor growth, a dual angiopoietin-2 (Ang-2)/VEGF-inhibiting antibody can significantly prolong survival in mice with glioblastoma by reprogramming M2 macrophages into the antitumor M1 phenotype [156]. However, there are no clinical data supporting the clinical application of bispecific antibodies in glioma patients.

As mentioned above, promising novel strategies are being developed, whereas combined therapy is another approach for improving the efficacy of immunotherapy [157]. For example, oncolytic viruses can destroy tumor cells, and then the released tumor lysates can stimulate immune responses, which might be enhanced by dendritic cell vaccines and immune checkpoint inhibitors [158,159]. Moreover, viruses can be utilized as vectors for transducing cytokine-encoding genes and other suicide genes to kill tumor cells [60,61]. However, combination of immunotherapies should be based on a thorough understanding of the underlying mechanisms. For instance, GM-CSF can be used as a cytokine therapy [160], whereas CSF inhibitors are used as a TAM-directed therapy. The combination of these two immunotherapies may exhibit antagonistic effects. Additionally, the safety and feasibility of combined immunotherapy should be carefully evaluated in clinical studies.

Given that various outcomes have been detected in patients with the same type of tumor treated with the same drug in the same tumor, personalized immunotherapy should be promoted as a future direction. Since MGMT gene promoter methylation has been investigated as a potential biomarker of sensitivity to alkylating chemotherapies, such as TMZ [161], there might be some potential genes indicating the sensitivity to immunotherapy. Moreover, pediatric gliomas are thought to be different from adult gliomas both biologically and histologically [162]. The immunotherapies that are effective against adult gliomas may not show efficacy in pediatric gliomas. During the evaluation of the efficacy of immunotherapy in glioma, it is best to set strict eligibility criteria defining the target population and make conclusions regarding the specific groups evaluated.

10. Conclusions

Recent years have witnessed great progress in fundamental and translational immunotherapy for cancer. The application of various immunotherapeutic approaches, especially combination strategies, has been proven to be efficacious against glioma. However, conflicting research findings indicate the necessity of performing additional studies to assess efficacy in specific patient groups.

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CRediT authorship contribution statement

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Declarations of competing interest

The authors declare that they have no competing interests.

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Abbreviations

CNS	central nervous system
WHO	World Health Organization
OS	overall survival
GBM	glioblastoma
IDH	isocitrate dehydrogenase
MGMT	O-6-methylguanine-DNA methyltransferase
FDA	Food and Drug Administration
PD-L1	programmed cell death 1 ligand
IDO	indolamine 2,3-dioxygenase
IL-10	interleukin 10
TGF-β	transforming growth factor β
TMZ	temozolomide
TTF	tumor-treating fields

Table 3
Ongoing clinical trials of CAR-T cell therapy in glioma.

Target	Study Number	Intervention	Disease	Phase	Primary Outcome Measures	Status
EGFR	NCT01454596	EGFRvIII CAR PBL, Aldesleukin, Fludarabine, Cyclophosphamide	Glioma, CNS Tumor	1, 2	TRAE, PFS	Completed
	NCT03638167	EGFR806 CAR-T	Glioma, CNS Tumor	1	TRAE, Feasibility	Recruiting
	NCT03283631	EGFRvIII CAR-T	GBM, GSM	1	MTD	Recruiting
	NCT03726515	EGFRvIII CAR-T, Pembrolizumab	GBM	1	TRAE	Recruiting
	NCT02664363	EGFRvIII CAR-T	GBM, GSM	1	MTD	Active, not recruiting
	NCT03389230	EGFR CAR-T	Glioma	1	TRAE	Recruiting
HER2	NCT03500991	HER2 CAR-T	Glioma, CNS Tumor	1	TRAE, Feasibility	Recruiting
IL13Rα2	NCT04003649	IL13Rα2 CAR-T + Nivolumab + Ipilimumab VS Nivolumab + IL13Ra2 CAR-T	GBM, GSM	1	DLT, CRS, Feasibility	Recruiting
	NCT02208362	IL13Rα2 CAR-T	Glioma, CNS Tumor	1	DLT	Recruiting
CD147	NCT04045847	CD147 CAR-T	GBM	1	TRAE	Active, not recruiting
GD2	NCT03252171	GD2 CAR-T	Glioma	1, 2	Overall Response	Completed
	NCT04099797	GD2 CAR-T, Cyclophosphamide, Fludarabine	Glioma	1	DLT	Not yet recruiting
EphA2	NCT02575261	EphA2 CAR-T	Glioma	1, 2	Tumor Volume	Completed
B7-H3	NCT04077866	TMZ + B7-H3 CAR-T VS TMZ + Placebo	GBM	1, 2	OS, PFS	Not yet recruiting

PBL: Peripheral blood lymphocytes; TRAE: Treatment related adverse events; PFS: Progression free survival; CNS: Central nervous system; GBM: Glioblastoma; GSM: Gliosarcoma; MTD: Maximum tolerate dose; DLT: Dose limiting toxicities; CRS: Cytokine release syndrome; OS: Overall survival.
*Clinical trials listed above have excluded those status being "unknown" and "terminated".

VEGF	vascular endothelial growth factor
GSC	glioma stem cell-like
NK	natural killer
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
HSV-TK	herpes simplex virus type 1 thymidine kinase
HGG	high-grade glioma
PFS	progression free survival
IFN	interferon
DCV	dendritic cell vaccine
APC	antigen-presenting cell
GM-CSF	granulocyte-macrophage colony-stimulating factor
EGFRvIII	epidermal growth factor receptor variant III
ATL	autologous tumor lysate
GAA	glioma-associated antigen
HLA	human leukocyte antigen
TAM	tumor-associated macrophages
MMP	matrix metalloprotease
CAR	chimeric antigen receptors
HER2	human epidermal growth factor receptor 2
ADCC	antibody-dependent cellular cytotoxicity
MHC	major histocompatibility complex
MAGE	melanoma-associated antigen
WT-1	Wilms' tumor protein

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