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Review article

New progress in the treatment of diffuse midline glioma with H3K27M alteration

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ABSTRACT

Diffuse midline glioma with H3K27 M alteration is a primary malignant tumor located along the linear structure of the brain, predominantly manifesting in children and adolescents. The mortality rate is exceptionally high, with a mere 1 % 5-year survival rate for newly diagnosed patients. Beyond conventional surgery, radiotherapy, and chemotherapy, novel approaches are imperative to enhance patient prognosis. This article comprehensively reviews current innovative treatment modalities and provides updates on the latest research advancements in preclinical studies and clinical trials focusing on H3K27M-altered diffuse midline glioma. The goal is to contribute positively to clinical treatment strategies.

1. Introduction

In 2016, WHO introduced a revised histological classification for malignant tumors of the central nervous system (CNS), incorporating the addition of diffuse midline glioma (DMG) with H3K27 M mutation [1]. The 2021 WHO classification further categorizes adult diffuse gliomas into three groups: astrocytoma (isocitrate dehydrogenase (IDH) mutant), oligodendroglioma (IDH mutant with 1p/19q codeletion), and glioblastoma (IDH wild type). Pediatric diffuse gliomas are classified into high-grade and low-grade categories. Pediatric diffuse high-grade gliomas encompass diffuse midline glioma (with H3K27 alteration), diffuse hemispheric glioma (H3G34 mutation), diffuse pediatric high-grade glioma (H3 and IDH wild-type), and infantile hemispheric glioma [2]. Diffuse midline gliomas with H3K27 M mutation primarily manifest in children and adolescents, and can also occur in adults. These lesions typically localize in midline structures (brain stem, thalamus, and spinal cord) and are characterized by the substitution of lysine with methionine at histone H3 lysine 27. This alteration results in an overall reduction in H3K27 trimethylation, an increase in H3K27 acetylation, and widespread oncogenic changes in gene expression, propelling the malignant progression of diffuse midline gliomas [3–5]. It is crucial to differentiate this from the new 2021 WHO definition of H3G34 mutant diffuse hemispheric glioma. H3G34 mutant diffuse hemispheric glioma is distinguished by the mutation of the H3F3A gene, leading to the conversion of glycine to arginine or valine at position 34 of histone H3.3. Pediatric diffuse midline gliomas with H3K27 M alteration, also known as diffuse intrinsic

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pontine glioma (DIPG), represent the most lethal subtype of DMG. The H3K27 M mutation is identified in approximately 80 % of DIPGs [6]. DMG with H3K27 M alteration exhibits highly aggressive biological behavior, posing significant challenges in its treatment. The H3K27 M status in DMG holds crucial therapeutic and prognostic implications for the disease [4,6–8]. Since the discovery of the molecular pathology of this tumor, numerous efforts have been dedicated to understanding its characteristics, resulting in significant advances. This review provides an overview of the latest progress in the treatment of H3K27M-mutated DMG, emphasizing targeted molecular therapy associated with H3K27M-altered DMG and potential therapeutic approaches beneficial for this tumor type.

1.1. Current treatment status and dilemmas

Diffuse midline gliomas with H3K27 M mutation, particularly DIPG, pose significant challenges as they are predominantly situated in midline locations such as the brainstem, and chemotherapy has proven to be ineffective [9]. While some centers utilize temozolomide as adjuvant therapy alongside radiotherapy, the role of temozolomide in DMG with H3K27 M mutation remains unclear. The high expression of O6-methylguanine DNA methyltransferase (MGMT) in DMG with H3K27 M mutation is known to confer resistance to temozolomide [4,10,11]. Consequently, radiation therapy stands as the sole standard treatment providing temporary symptom relief, delaying disease progression, and extending median survival by several months. Tumor treatment fields (TTFields), known to prolong the survival of glioblastoma (GBM) patients, have received approval from the US Food and Drug Administration (FDA) for the treatment of recurrent and newly diagnosed GBM after surgery and adjuvant temozolomide (TMZ) radiotherapy [12–15].

Despite the rapid advancement in current therapeutic approaches, the availability of drugs for treating DMG with H3K27 M mutation remains limited. A key obstacle to progress is the presence of the blood-brain barrier, composed of endothelial cells, capillaries, and basement membranes, which restricts the entry of most antitumor drugs into the brain [16–18]. Gliomas can express various immunosuppressive factors, including programmed cell death ligand 1 (PD-L1), indoleamine 2,3-dioxygenase (IDO), and others. Elevated levels of these immunosuppressive factors in glioma cells hinder antigen presentation [19,20]. Interleukin-10 (IL-10) and transforming growth factor β (TGF-β), secreted by associated macrophages in the tumor microenvironment, inhibit immune clearance by attenuating the activity of immune cells in the vicinity [18,21]. Additionally, regulatory T cells in the tumor microenvironment induce immunosuppression by depleting cytotoxic T lymphocytes [22,23]. Consequently, there is an urgent need for improved treatments for H3K27M-altered DMG to enhance patient survival.

2. Therapy

2.1. CAR-T therapy

Chimeric antigen receptor (CAR) is a modular fusion protein, genetically engineered as an immunoglobulin T-cell receptor molecule comprising extracellular, transmembrane, and intracellular domains [24–27]. Eshhar and Kuwana et al. pioneered the engineering of CAR-expressing T cells through gene transfer, utilizing single-chain variable fragments (scFv) to bind to the domain for specific target antigen recognition. Notably, CD3ζ serves as the master switch for T cell activation, enabling T cell activation independent of major histocompatibility complex (MHC) activation [28–30].

CAR T-cell therapy, which targets the CD19 antigen, a B-cell biomarker, has gained FDA approval for treating B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma [31,32]. Subsequently, CAR T-cell therapy has been extensively explored for various solid tumors, including breast cancer, glioma, liver cancer, with CARs designed to target CD19, IL13Rα2, EGFRvIII, HER2, and CD70 [33,34].

In 2018, Christopher et al. identified elevated GD2 expression in DIPG and demonstrated promising preclinical efficacy of GD2-directed CAR T-cell therapy [35]. Immunotherapy targeting GD2 has been investigated clinically and preclinically in patients with neuroblastoma, osteosarcoma, and melanoma [36–41]. Despite promising preclinical efficacy, serious adverse effects, such as hydrocephalus due to peritumor neuroinflammation during the acute phase of antineoplastic therapy, must be addressed for the successful implementation of GD2-targeted CAR T-cell therapy in the clinic. The phase I human clinical trial of GD2 CAR T-cell therapy (NCT04196413), published in Nature in 2022, reported the first clinical trial in four H3K27M-mutated DMG patients. Initial treatment involved intravenous GD2 CAR T-cells, and those exhibiting clinical benefit underwent subsequent intraventricular GD2 CAR-T cell treatment. Three out of four patients demonstrated clinical and radiographic improvement, suggesting a promising therapeutic prospect for H3K27M-mutated DMG [42].

In conclusion, GD2-targeted CAR T-cell therapy proves beneficial for H3K27M-mutant DIPG. CAR T-cells precisely target tumor cells, improving efficacy and reducing toxicity. However, the management of adverse reactions remains a primary concern, necessitating close monitoring and proper intervention.

2.2. Histone deacetylase inhibitor treatment

Histone acetylation plays a crucial role in gene expression, with acetylation generally associated with increased gene expression, while deacetylation correlates with decreased gene expression [43]. Consequently, the modulation of histone acetylation and deacetylases serves as a key mechanism for controlling gene expression levels. Over the past decade, histone deacetylase inhibitors (HDACi) have emerged as significant agents in clinical trials across various disease types [44]. The therapeutic impact of HDACi in tumor treatment stems from its broad anticancer effects, including the induction of differentiation, cell cycle arrest, apoptosis, and inhibition of angiogenesis [43]. Grant L et al. substantiated the combination of the multi-histone deacetylase inhibitor Panobinostat

and the proteasome inhibitor Marizomib as a promising therapeutic approach through a serial high-throughput screen. Transcriptomic and metabolomic studies revealed substantial changes in key metabolic processes and cellular unfolded protein responses following Panobinostat and Marizomib treatment. Subsequent investigations indicated that metabolic abnormalities induced cytotoxicity, thereby promoting tumor cell death [45]. This study introduces a novel single-agent and combination treatment option for DMG and underscores the feasibility of a combined treatment strategy involving HDACi and proteasome inhibitors.

Furthermore, it has been observed that Panobinostat treatment reduces the expression of scaffold proteins EBP50 and IRSp53, thereby inhibiting the proliferation, migration, and invasion of DMG cells while enhancing apoptosis [46]. This further underscores the potential of HDACi in cancer treatment.

Nicholas A et al. utilized clinically relevant DMG models in preclinical studies to identify and validate other biomarkers indicative of a biological response following HDACi treatment. Quisinostat and romidepsin were identified as inhibitors that effectively curbed tumor growth in vivo [47]. A 2022 study investigating combined treatment with mitochondrial casein-lytic peptidase P (ClpP) protease and HDAC inhibitor activation by imidinone compounds demonstrated that this combined approach significantly prolonged the survival of patient-derived xenograft (PDX) mice compared to monotherapy [48]. In conclusion, the development of HDACi presents a promising therapeutic avenue for DMG, addressing the treatment challenges associated with diffuse midline gliomas, a malignancy currently lacking effective therapeutic options.

2.3. Enhancer of Zeste homolog 2 inhibitor treatment

As previously discussed, the epigenome is subject to various modifications, encompassing processes such as DNA methylation, histone acetylation, histone phosphorylation, histone methylation, and other post-translational modifications. Mutations in enzyme systems governing the epigenome can precipitate a cancer-like state, exerting profound effects [44]. Enhancer of Zeste homolog 2 (EZH2), a catalytic subunit of histone methyltransferase, plays a pivotal role in catalyzing the monomethylation, dimethylation, and trimethylation of histone H3 lysine 27. This activity induces hypermethylation of downstream target genes, resulting in the silencing of tumor suppressor genes and fostering tumor progression [49]. Notably, the H3K27 M mutation leads to H3K27 hypomethylation, impacting gene transcription and contributing to cancer development. The interplay between EZH2 and H3K27 M mutation promotes tumor progression [50].

In 2020, the FDA granted approval for tazemetostat, the world's first EZH2 inhibitor, for the treatment of inoperable, metastatic, or locally advanced epithelioid sarcoma [51]. Faizaan Mohammad et al. at the University of Copenhagen developed a mouse model wherein H3K27 M mutations enhance tumors. They demonstrated that Polycomb Repressive Complex 2 (PRC2) is essential for the proliferation of tumors expressing H3K27 M, and further showed that a small-molecule EZH2 inhibitor halted tumor cell growth by inducing the tumor suppressor protein p16Ink4a [50]. Collectively, these findings suggest that inhibiting EZH2 holds promise as a therapeutic strategy for tumors characterized by H3K27 M mutations.

2.4. ONC201 and its derivative therapy

ONC201 is a small molecule drug with the capability to penetrate the blood-brain barrier. Its core structure, imipridone, targets mitochondrial function and exerts its effects by antagonizing dopamine receptor D2 (DRD2) and/or over-activating the protein lytic activity of ClpP [52,53]. Notably, it has demonstrated exceptional efficacy in patients with gliomas harboring a specific gene mutation, the histone H3K27 M mutation [54]. This efficacy was further evident in a 22-year-old patient with H3K27M-mutated DMG [4].

Following the initial treatment of the first patient with H3K27M-mutated diffuse midline glioma with ONC201 (NCT02525692), an expanded enrollment protocol was initiated. Subsequently, 18 patients with H3K27M-mutated diffuse midline glioma or DIPG were enrolled. Investigators reported radiographic resolution or complete response of thalamic and pontine gliomas, along with disease-related improvement in neurological symptoms [54]. A phase 1 clinical study of ONC201 in the treatment of H3K27 M mutant DMG (NCT03416530), published in 2022, aimed to evaluate the therapeutic effect of ONC201 by analyzing free tumor DNA in serial lumbar puncture specimens and plasma samples. The study found that cell-free tumor DNA in plasma and cerebrospinal fluid (CSF) could predict ONC201 treatment response and progression in DMG patients [55].

Moreover, Isabel Arrillaga-Romany et al. treated 6 adult patients with recurrent glioblastomas and 20 patients with recurrent glioblastomas who did not undergo surgical resection with ONC201. The study suggested that ONC201 may be biologically active in patients with recurrent glioblastoma and was well-tolerated. was well-tolerated. Multifocal H3K27M-mutant glioblastoma in an adult patient treated with ONC201 showed a significant radiographic response [56]. This offers a potential basis for ONC201 in the treatment of H3K27 M mutant diffuse midline gliomas.

A recent clinical study demonstrated the efficacy of ONC201 in 71 DMG patients with H3K27 M mutation, resulting in a significantly prolonged survival time. The median overall survival (mOS) for patients receiving first-line ONC201 treatment was 21.7 months, a remarkable improvement of 9.7 months over historical controls. Additionally, nearly one-third of patients lived longer than 2 years [57].

To enhance the efficacy and safety of treating diffuse midline gliomas, the second generation of imidazole drugs, including ONC206 and ONC212, has emerged. Both ONC201 and ONC206 can directly bind to ClpP. A study in 2022 compared the relative efficacy of ONC201 and ONC206, revealing that both reduced the viability of DMG cells and prolonged the survival time of PDX models of diffuse midline glioma. Notably, the in vitro potency of ONC206 was found to be 10 times stronger than that of ONC201 [58]. As mentioned in Section 2, the activation of mitochondrial ClpP protease by imidinone compounds (ONC201, ONC206, ONC212) in combination with HDAC inhibitors improves host survival [48].

Additionally, a study investigated whether the combination of imidazole and other drugs surpassed single drug treatment in H3K27 M mutant DIPG cell lines. The results indicated that combination treatment was superior to single drug treatment, with the second generation of imidazole proving more effective against H3K27 M mutant DIPG. Notably, ONC206 has entered phase I clinical trials for malignant solid tumors, including glioblastoma (NCT04541082), and clinical trials for diffuse midline glioma (NCT0500992, NCT04732065).

2.5. Tumor treatment field treatment

Tumor Treating Fields (TTFields) represent noninvasive anticancer therapies utilizing alternating electric fields within the range of 100–300 kHz to selectively disrupt the mitosis of cancer cells. TTFields directly target crucial proteins in the cell cycle, leading to mitotic arrest and subsequent cell death [12,59–61]. Preclinical models suggest that, aside from inhibiting cancer cell proliferation through the disruption of the mitotic spindle, causing delayed mitosis or cell death, TTFields also interfere with DNA repair mechanisms. Furthermore, TTFields have been shown to enhance chemotherapy sensitivity by increasing cell permeability and inducing autophagy [12].

Combining TMZ with TTField therapy has demonstrated a significant prolongation of overall survival (OS) and progression-free survival (PFS). In one case, a 3-year-old child with diffuse midline glioma underwent concurrent chemoradiotherapy with TMZ, followed by maintenance therapy with TTFields combined with TMZ. The results indicated an initially poor response to TTFields, which gradually improved over time. This suggests that discontinuing TTFields treatment may not be necessary even if the initial response is unsatisfactory. Instead, patients should be encouraged and supported to enhance their adherence to long-term treatment [62].

Table 1
Related ongoing clinical trials registered at ClinicalTrials.gov.

Study Name	NCT Number	phase	Start Year	intervention	statue
Trial of Panobinostat in Children with Diffuse Intrinsic Pontine Glioma (PBTC-047)	NCT02717455	I	2016-06-28	Drug: LBH589	Active, not recruiting
Study of B7–H3-Specific CAR T Cell Locoregional Immunotherapy for Diffuse Intrinsic Pontine Glioma/ Diffuse Midline Glioma and Recurrent or Refractory Pediatric Central Nervous System Tumors	NCT04185038	I	2019-12-11	Biological: SCRI-CARB7H3(s); B7H3-specific chimeric antigen receptor (CAR) T cell	Recruiting
GD2 CAR T Cells in Diffuse Intrinsic Pontine Gliomas (DIPG) & Spinal Diffuse Midline Glioma (DMG)	NCT04196413	I	2020-06-04	Drug: GD2 CAR T cells Drug: Fludarabine Drug: Cyclophosphamide	Recruiting
A Study of BXQ-350 in Children with Newly Diagnosed Diffuse Intrinsic Pontine Glioma (DIPG) and Diffuse Midline Glioma (DMG)	NCT04771897	I	2021-05-24	Drug: BXQ-350	Recruitting
Non-Invasive Focused Ultrasound (FUS) With Oral Panobinostat in Children with Progressive Diffuse Midline Glioma (DMG)	NCT04804709	I	2021-07-28	Drug: Panobinostat 15 MG Device: Focused Ultrasound with neuro-navigator-controlled sonication	Active, not recruiting
ONC206 for Treatment of Newly Diagnosed, Recurrent Diffuse Midline Gliomas, and Other Recurrent Malignant CNS Tumors (PNOC023)	NCT04732065	I	2021-08-23	Drug: ONC206 Radiation: Standard of Care Radiation Therapy	Recruiting
Stereotactic Biopsy Split-Course Radiation Therapy - Diffuse Midline Glioma (SPORT-DMG)	NCT05077735	II	2021-10-06	Radiation: Hypofractionated Radiation Therapy Other: Quality-of-Life Assessment Other: Questionnaire Administration	Recruitting
rHSC-DIPGVax Plus Checkpoint Blockade for the Treatment of Newly Diagnosed DIPG and DMG	NCT04943848	I	2022-01-10	Biological: rHSC-DIPGVax Drug: Balstilimab Drug: Zalifrelimab	Recruiting
A Study of Avapritinib in Pediatric Patients with Solid Tumors Dependent on KIT or PDGFRA Signaling	NCT04773782	I-II	2022-02-24	Drug: avapritinib	Recruiting
ONC201 in H3 K27M-mutant Diffuse Glioma Following Radiotherapy (the ACTION Study) (ACTION)	NCT05580562	III	2023-01-23	Drug: ONC201 Drug: ONC201 + Placebo Other: Placebo	Recruiting
FUS Etoposide for DMG - A Feasibility Study	NCT05762419	I	2023–03	Drug: Etoposide; Oral, 50 Mg Device: Focused ultrasound with neuro-navigator-controlled sonication	Recruiting
Study of B7–H3, EGFR806, HER2, And IL13-Zetakine (Quad) CAR T Cell Locoregional Immunotherapy for Pediatric Diffuse Intrinsic Pontine Glioma, Diffuse Midline Glioma, And Recurrent or Refractory Central Nervous System Tumors	NCT05768880	I	2023-05-05	Biological: SC-CAR4BRAIN	Recruiting
CAR T Cells to Target GD2 for DMG (CARMIGO)	NCT05544526	I	2023-08-15	Biological: GD2 CAR T cells	Recruiting

Although there is currently no specific study on TTFields in the treatment of H3K27 M mutant diffuse midline gliomas, a case report revealed that a patient with H3F3A mutation and IDH wild-type diffuse midline glioma had an extended survival time after concurrent chemoradiotherapy and TTFields treatment [63]. This observation provides reason to believe that TTFields treatment may confer significant benefits for H3K27 M mutant diffuse midline gliomas.

2.6. PD-1/PD-L1 treatment

Immune checkpoint inhibition has revolutionized the treatment landscape for various tumors, such as lymphoma, renal cancer, melanoma, and lung cancer, contributing to increased median survival in patients with these malignancies [64–67]. Immune checkpoint inhibitors, including programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and others, exhibit the ability to activate the normal immune system, thereby enhancing its strength [68,69]. However, the tumor microenvironment of DMG is characterized by immunosuppression and impaired immune surveillance, presenting significant challenges for this form of treatment [70].

In a single-center clinical trial, a retrospective cohort analysis was conducted on children with recurrent DIPG treated with re-irradiation (reRT) at recurrence, with or without PD-1 inhibition. The results demonstrated that OS in patients treated with reRT combined with PD-1 inhibitor was extended by 22.9 months compared to reRT alone. This suggests that the combination of reRT and PD-1 inhibitor provides a survival benefit for patients with recurrent DIPG [71]. Given the limited active immune penetration in DMG, the use of PD-1/PD-L1 inhibitors alone may not be highly effective, and OS improvement may be limited. However, combining these inhibitors with other targeted therapies may yield more promising results [72]. Numerous studies on PD-1/PD-L1 immunotherapy for gliomas have been registered on ClinicalTrials.gov (Table 1).

2.7. Cytokine therapy

Cytokines, produced by the immune system, play a crucial role in regulating immune responses. Tumors often exploit cytokines as

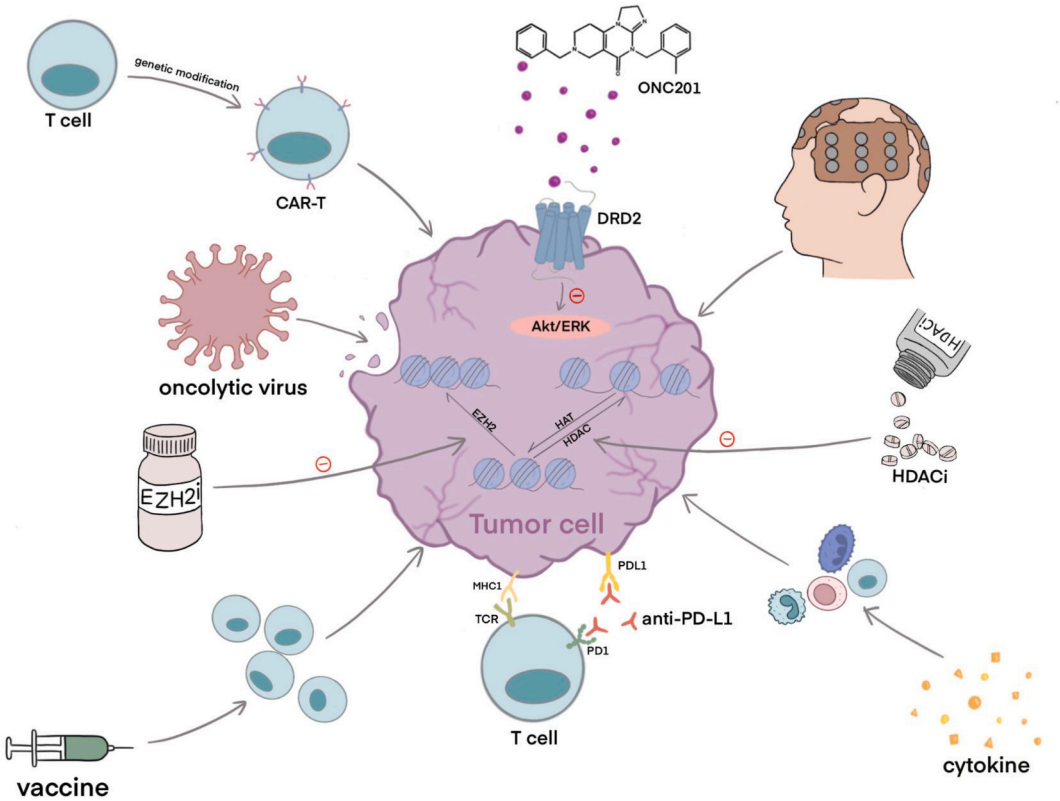

Fig. 1. Therapeutic strategies for H3K27 M mutation DMG. CAR T-cells can precisely target and kill tumor cells. HDACi exerts anticancer effects by inducing differentiation, cell cycle arrest, apoptosis and inhibiting angiogenesis. EZH2 inhibitors inhibit tumor growth by a mechanism dependent on the induction of tumor suppressor proteins. ONC201 and its derivatives exert their effects by antagonizing the dopamine receptor D2 (DRD2) and/or over-activating the protein lytic activity of caseinolytic peptidase P(ClpP). TTFields directly target proteins essential for the cell cycle, arresting mitosis and causing cell death. Tumor vaccines attack tumors by inducing an immune response. Oncolytic viruses selectively infect and kill tumor cells.

protective mediators to dampen the immune response. However, the immunomodulatory effects induced by these cytokines can also be harnessed to trigger an immune response against tumor cells [73]. Among the cytokines utilized in cancer therapy, interleukins and interferons stand out, being FDA-approved for such applications [74].

A pivotal tumor necrosis factor-related activator protein is CD40 ligand (CD40L), which plays a crucial role in tumor immunity. By binding specifically to its receptors CD40 and CD40L, it contributes to direct killing of tumor cells, inflammation, and other pathological responses [75]. Utilizing an adenovirus expressing CD40 ligand (AD-CD40L) to treat homologous gliomas implanted in the brainstem of immunocompetent mice suggested that virus-mediated CD40L presentation might be effective in diffuse midline gliomas without inducing mandatory neuroinflammatory toxicity [76].

Additionally, James et al. observed that PDGFA-induced tumors significantly improved median survival and reduced tumor-associated macrophage (TAM) infiltration compared to PDGFB. Further studies revealed that PDGFB-driven tumors exhibited a highly inflammatory microenvironment characterized by high expression of the CCL3 chemokine [77]. These findings suggest that cytokine preparations can stimulate specific immune responses, enhance tumor cell apoptosis, and inhibit tumor cell proliferation (Fig. 1). However, further clinical studies are necessary to validate these observations.

2.8. Vaccine therapy

Tumor vaccines operate by triggering an immune response against tumors, and they have been subject to extensive investigation as potential therapies for gliomas. In a clinical trial assessing the safety and efficacy of tumor vaccines, a previously identified synthetic peptide vaccine named H3.3K27 M was tested in patients diagnosed with DIPG or other DMG carrying H3.3K27 M mutations and HLA-A*02:01 mutations (NCT029960230). The results demonstrated that the specific vaccine was well-tolerated, leading to a significant prolongation of patients' overall survival [78].

In 2021, Michael Platten et al. reported the initial findings of a multicenter, single-group, open-label phase I clinical trial (NCT02454634) involving glioma patients. In this study, 33 patients diagnosed with IDH-mutant astrocytoma were vaccinated with an IDH1- specific peptide vaccine (IDH1-vac). Notably, vaccine-induced immune responses occurred in 93.3 % of these patients, resulting in a 2-year progression-free rate of 0.82 and a 3-year mortality-free rate of 0.84, with no serious adverse events [79]. These promising results instill confidence and lay the groundwork for future vaccine trials in the realm of cancer immunotherapy.

2.9. Oncolytic viruse therapy

Oncolytic Viruses (OVs) are a class of viruses with the ability to selectively infect and eliminate tumor cells. They possess specific replication capabilities and can stimulate the body to mount an anti-tumor immune response. OVs mainly fall into two categories: natural virus strains and genetically modified virus strains. The therapeutic goal is achieved through the virus's specific infection of tumor cells and the subsequent release of viral progeny, inducing tumor cell lysis [80].

A previously conducted adenovirus, DNX-2401 (Delta-24-RGD), demonstrated safety and efficacy in a DMG patient-derived xenograft mouse model and underwent testing in a phase I clinical trial (NCT03178032) [81,82]. In a subsequent phase I clinical trial, among 11 patients treated with DNX-2401 particles followed by radiotherapy, three showed partial responses, eight exhibited stable disease, and the median survival was 17.8 months. Autopsy and peripheral blood tumor samples revealed significant changes in the tumor microenvironment and T cell pool, suggesting that DNX-2401 virus particles provide a notable survival benefit with relative safety in treating DIPG [83].

Moreover, a phase II single-center clinical trial initiated by Japanese investigators in 2022 assessed the efficacy of oncolytic herpesvirus G47Δ in treating residual or recurrent glioblastoma (UMIN-CTR Clinical Trial Registry UMIN000015995). After repeated intratumoral administrations, magnetic resonance imaging revealed recurrent patterns of enlargement and clear enhancement in the lesion after each dose. Biopsy results showed increased numbers of tumor-infiltrating CD4/CD8 lymphocytes, with consistently low Foxp3 cell numbers, indicating a favorable safety benefit and safety profile [84].

In addition, herpes simplex virus 1716 (HSV1716) has demonstrated anti-tumor activity against DMG, showing harmlessness to normal nerve cells and reducing tumor invasion in an orthotopic mouse model of DMG [72,85]. Although no results related to oncolytic HSV1716 have been presented to date, another oncolytic adenovirus, CRAd.S.pK7, encapsulated in mesenchymal stem cells, has made progress in mouse models through intratumoral injection, addressing oncolytic virus transmission issues in tumors and improving the efficacy of subsequent radiotherapy [72,86].

2.10. Chemotherapy and radiotherapy

Chemotherapy has not demonstrated efficacy in treating H3K27M-mutated DMG [9]. While TMZ has shown immunomodulatory effects in glioblastoma, its effectiveness in DMG remains unproven. Chemotherapy is often employed in combination with other treatments. Radiation therapy is considered clinically beneficial for DMG, and a previous study indicated that combining radiation therapy with IDO inhibitors and PD-1 inhibitors increased survival in mice, suggesting a potential survival benefit of radiation therapy combined with immune checkpoint inhibitor (ICI) therapy in glioblastoma [87]. Other preclinical models exploring combination therapies, such as the synergy between radiotherapy and CAR-T therapy, have been investigated [88]. However, there is a lack of studies examining the combination of radiotherapy with other treatments specifically in the context of DMG.

3. Challenges and prospects

Many therapies have proven ineffective against H3K27M-mutant DMG. Given that treatment decisions hinge on the molecular diagnostic type of the tumor, identifying an accurate method for determining the tumor type is crucial. Liquid biopsy has emerged as a viable method for detecting H3K27 M mutations in DMG [4,89,90]. Similarly, post-treatment monitoring is essential. Circulating tumor DNA (ctDNA) has been successfully utilized to monitor disease progression in various adult cancers, including liver, lung, and breast cancers, and is gaining traction in the pediatric CNS population [91–93]. ctDNA released by brain tumor cells can traverse the blood-brain barrier into the cerebrospinal fluid and plasma, holding significant clinical application value for disease diagnosis and treatment monitoring [94]. Furthermore, ctDNA can function as an early biomarker of disease progression, potentially detecting tumor changes before they become apparent on MRI scans, enabling earlier and more precise clinical treatment planning [4,93,95,96]. However, it is crucial to note the potential clinical safety risks associated with a burst of immune activation after therapy, including cytokine release syndrome (CRS) and neurotoxicity [97,98].

Despite the absence of a definitive effective treatment for H3K27 M DMG and its generally poor prognosis, several clinical trials show promising expected results. The future may witness significant progress in combination therapies for H3K27M-mutant DMG. Nevertheless, it is imperative to monitor adverse reactions diligently and evaluate any changes in the patient's condition during treatment. With an increasing understanding of H3K27M-mutant DMG, there is optimism that treatment outcomes for DMG with H3K27 M mutations will improve in the future.

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CRediT authorship contribution statement

Zhi Yang: Writing – review & editing, Writing – original draft, Methodology. **Liang Sun:** Methodology. **Haibin Chen:** Investigation. **Caixing Sun:** Writing – review & editing. **Liang Xia:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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