



Review

Oncolytic virus therapy for glioma: current clinical trials and overcoming key obstacles

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Highlights

- A novel review of recent glioma oncolytic virus trials, analyzing viral vectors, delivery optimization, and immune modulation to enhance clinical translation.

- A systematic review of single-agent oncolytic virus trials for glioma, comparing efficacy and safety profiles across different viral types.
- This work details methods to improve oncolytic virus delivery efficiency, offering solutions to overcome key challenges in treatment.
- An in-depth study of oncolytic virus combined with chemo-/radio-/immunotherapy, proposing improved clinical management strategies.

Abstract

The poor prognosis of glioma underscores the urgent need for novel therapies. Recent advances in immunotherapy, especially in oncolytic virus therapy (OVT), have shown promising progress. In clinical trials, OVT has improved median overall survival up to 28.8 months. Different oncolytic viruses, including herpes simplex virus (HSV), adenoviruses, and polioviruses, have shown varying efficacy. HSV-based therapies, like G47 Δ , have demonstrated promising survival outcomes, whereas polioviruses like PVSRIPO have excelled in eliciting strong immune responses. However, key challenges include ensuring the safety of viral vectors, overcoming the blood-brain barrier, maintaining long-term efficacy, and addressing excessive inflammation. This review aims to summarize the clinical challenges of OVT in glioma, with a focus on safety, delivery methods, immune response modulation, and the efficacy of various viruses.

Introduction

Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults, and is characterized by a dismal prognosis with a five-year relative survival rate of approximately 5.5% [1]. However, the standard of care rarely achieves durable clinical benefits [2]. Therapeutic failure is driven by multiple factors, including profound inter- and intratumoral heterogeneity, the restrictive nature of the blood-brain barrier (BBB), and a deeply immunosuppressive tumor microenvironment (TME) [3]. Therefore, novel therapeutic strategies are urgently needed.

Immunotherapy, which aims to leverage the host immune system to treat malignancies, has emerged as a promising therapeutic modality for GBM [4]. Among these immunotherapeutic strategies, oncolytic virotherapy (OVT) holds particular promise because of the inherent or engineered tropism of oncolytic viruses (OVs) for tumor cells [5]. In addition to direct oncolysis, OVs function as potent in situ vaccines capable of remodeling the immunologically 'cold' TME [6]. This immunomodulation is initiated by the induction of immunogenic cell death (ICD), which triggers the release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs), ultimately leading to DC maturation, effector T-cell recruitment, and the reversal of local immunosuppression [7,8].

Indeed, OVT has shown notable promise in clinical settings. For example, early-phase trials of

G47Δ in recurrent GBM (rGBM) reported median overall survival (mOS) rates of approximately 28.8 months after OVT, a significant extension compared with historical controls [9,10]. A pivotal breakthrough occurred in 2021 with the conditional approval of G47Δ in Japan for the treatment of malignant glioma, validating the feasibility of this approach [11]. In the United States, several candidates have achieved through clinical trials, with both DNX-2401 and PVSRIPO receiving Orphan Drug and Breakthrough Therapy designations from the FDA for rGBM [12]. Therefore, this review synthesizes the current clinical landscape of OVT for glioma. We will critically analyze the key challenges and opportunities related to viral vector selection, delivery strategies, and the modulation of the host antitumor immune response. Ultimately, we aim to provide a forward-looking perspective on optimizing OVT to improve outcomes for patients with gliomas.

Section snippets

Therapeutic mechanism of oncolytic viruses.

The therapeutic action of OV is multifaceted. Initially, OVs selectively replicate within and lyse tumor cells, a process known as oncolysis. This direct cytotoxic effect also serves to initiate a robust antitumor immune response through the release of TAAs, effectively leading to durable, systemic immunity (Fig.1). ...

Clinical development of oncolytic virotherapy for glioma.

To date, numerous clinical trials have investigated the potential of OV monotherapy for patients with gliomas. We identified 32 clinical trials, the key findings of which are summarized in Table 1, Table 2. ...

Intratumoral injection

Intratumoral injection is the most established route of administration for OVs. This approach is advantageous because it directly addresses the unique anatomical characteristics and dense tissue composition of gliomas, which severely limits viral diffusion [112]. By delivering the agent locally, high titers can be achieved, reducing the neutralizing effect of viral antibodies and preventing off-target toxicity due to systemic distribution.

However, considering the diffuse distribution of gliomas ...

Rational combinations: sensitizing standard therapies and modulating the TME

Owing to resistance to multiple drugs and aggressive progression of glioma, it is necessary to combine OVs with other therapeutic modalities to increase their efficacy. Currently, radiotherapy and chemotherapy are deeply rooted in combined treatments. Additionally, immunotherapies,

such as ICIs, hold significant promise. Complete information can be found in Table 4. ...

Overcoming key obstacles: from bench to bedside

A review of current clinical trials revealed that the path for OVT from basic research to clinical application is fraught with numerous hurdles that collectively limit its development.

The complexity of efficacy assessment, centered on the phenomenon of pseudoprogression, is a common obstacle for clinical trials for brain tumors. Currently, MRI is the most common radiographic tool for clinical evaluation. However, in some trials, such as those involving G47Δ, the intense immune response induced ...

Patient consent for publication

Not applicable. ...

CRedit authorship contribution statement

Xiaoke Zhang: Writing – original draft, Data curation, Conceptualization. **Yanfeng Li:** Data curation. **Nanxi Liu:** Writing – original draft, Data curation, Conceptualization. **Yunfan Zhang:** Data curation. **Nian Yang:** Data curation. **Liangxue Zhou:** Writing – review & editing, Funding acquisition. ...

Ethics approval and consent to participate

Not applicable. ...

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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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