Targeting Glioma with Oncolytic Viruses: Emerging Possibility in Overcoming Treatment Limitations – A Review

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Abstract

Glioma tumors are considered to be an aggressive and lethal type of cancer. Malignant gliomas continue to have a poor prognosis; the five-year survival rate for the patients with early-stage diagnosis is only 5%, despite the fact that vigorous standard therapy is provided, such as surgical resection and chemo-radiotherapy. In light of this, recent developments using new immunotherapeutic techniques aim to address the treatment of glioblastoma. Oncolytic immunotherapy (OVT) is a recent advancement for the treatment of these types of cancers. OVT is an anticancer therapeutic approach in which viruses reproduce and propagate across tumors, while killing tumor cells in a selective and preferential manner. Administering OVTs can cause an increased number of immune cells to enter into the center of tumors to reshape their microenvironment and synchronize with other immunotherapies better. By causing apoptosis or eliciting an immune response against the tumor, a number of oncolytic viruses have shown a capacity to selectively infect and kill glioma cells. In the subsequent sections, we explored the function of oncolytic virotherapy in malignant gliomas, emphasizing recently completed and continuing clinical investigations, as well as obstacles faced using this therapeutic approach. Effectual treatment modalities for malignant gliomas are made challenging by the fact that they are heterogeneous tumors as well as due to the tumor microenvironment (TME) and the blood-brain barrier (BBB). Therefore, the potential advancements that could occur in the context of this area have been reviewed.

Keywords: Glioma, Immunotherapy, Treatment, Limitation, Oncolytic Virotherapy

Significance | Diffuse glioma, notably glioblastoma, poses immense treatment challenges due to its invasiveness, genetic variability, and resistance, necessitating innovative therapeutic strategies.

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Introduction

Diffuse glioma ranks as the most prevalent type of central nervous system (CNS) tumor, known for its invasive growth, encompassing astrocytomas, oligodendrogliomas, and oligoastrocytomas (Ostrom et al., 2019). The World Health Organization (WHO) employs a classification system for these tumors based on their histological and molecular characteristics. Glioblastoma (GBM), identified as the most malignant form of glioma, accounts for over half of all glioma cases. It also has one of the highest mortality rates among primary brain tumors (Ostrom et al., 2018). Annually, there are 4.32 cases of glioblastoma per 100,000 people in the US (Davis et al., 2019), highlighting its prevalence and lethality. The aggressive character of this tumor, together with genetic variability, the often recurrence and the difficulty in maintaining effective chemotherapy levels which is caused by blood-brain barrier (BBB), highlight the great medical needs for glioma patients (Jackson et al., 2019).

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In clinical settings, immunotherapy has recently demonstrated its potential when combined with the immune checkpoint inhibitors (ICIs), such as PD-1 that blocks programmed cell death 1 (PD-1) or CTLA-4 which prevents the binding of its corresponding receptor (Suryawanshi & Schulze, 2021). Such therapeutic approaches are now often used to treat many different kinds of cancer. Although ICIs have been demonstrated to be beneficial in patients in an expanding range of tumor types, significant heterogeneity persists in the extent and duration of immune checkpoint inhibitor (ICI) response within solid tumors. Even though the degree of tumor mutation burden (TMB), checkpoint ligand expression and faulty DNA repair mechanism (Le et al., 2017) have been essential to predict the efficacy of ICIs; nevertheless, the ability to accurately predict individual responses to ICIs remains primarily restrained due to the complex correlation between cancer cells and the immune system. The use of chimeric antigen receptor (CAR) T cells has become a potentially effective treatment for malignant gliomas. However, the presence of several immune suppressive antigens produced by tumor cells may impede the effectiveness of CAR T cell treatment and cancer vaccines, resulting in an off-target impact and decreased anticancer efficacy (Suryawanshi & Schulze, 2021).

Second-line treatments are still being tested and refined despite the fact that several ways are being investigated to circumvent therapeutic resistance. While anti angiogenic drugs like bevacizumab may improve patients' quality of life, they do little to improve their overall survival (OS). In addition, there are no novel therapies for glioma that have been validated by the US Food and Drug Administration (US FDA) (Rius-Rocabert et al., 2020). Numerous factors contribute to treatment difficulties, including as a high propensity for invasion and infiltration, numerous pathways of resistance, and significant heterogeneity both within and across tumors. Moreover, a subset of cancer stem cells (CSCs) is thought to be in charge of spreading tumor cells through healthy brain parenchyma, which aids in the development and recurrence of gliomas.

Recently, oncolytic virotherapy (OVT) is widely regarded as a promising option for treating cancer (Wollmann et al., 2012). IMLYGIC™ (Talimogene Laherparepvec or T-VEC) is a genetically engineered oncolytic Herpes Simplex Virus armed with granulocyte-macrophage colony-stimulating factor (GMCSF) approved by the US FDA for the treatment of nonresectable melanoma (Bommareddy et al., 2017). In this approach, replication-competent viruses are used in oncolytic virotherapy because of their ability to selective replication and lysis. Here, cancer cell death is cause by oncolytic viruses (OVs) in a variety of ways, including apoptosis, pyroptosis, and necroptosis (Suryawanshi & Schulze, 2021). Both the viral progeny and the danger-associated molecular patterns (DAMPs) that trigger the body's innate and adaptive immune responses are greatly elevated when replicative viruses are employed for OVT. Through the formation of selective immunogenic cell death (ICD), tumor infection promotes tumor eradication and sets off an antiviral and antitumor-specific immune response (Rius-Rocabert et al., 2020). Moreover, OVT may be selected or altered genetically to decrease their toxicity and/or increase their tumor immunogenicity, making them tumor-specific.

During viral infection, the host cell's pattern recognition receptors (PRRs) identify pathogen-associated molecular patterns (PAMPs) (Rius-Rocabert et al., 2020). The innate immune system of the body is stimulated by these receptors, leading to the production of proinflammatory cytokines such as IL-1, tumor necrosis factor (TNF), and interleukin (IL)-6, as well as interferons (IFNs), which in turn promote an antiviral state within the tumor microenvironment.. However, it is well-established that certain cancer cells are incapable of eliciting this kind of immune-mediated response. These tumor cells have a higher susceptibility to oncolysis caused by viral replication. Infection with a virus may also encourage an antiviral response that influences the environment around the tumor. Hence, the OVT efficacy is determined by the interplay of the direct tumor cell destruction caused by tumor specific viral replication with the virus and tumor specific cytotoxic T lymphocyte (CLT) responses.

OV are the good candidates for boosting the immune cells infiltration and causing inflammation within the tumor microenvironment (TME). This step is important for overcoming the immune tolerance and enhancing how tumors respond to the ICIs (Hong Jae Chon et al., 2018). To be precise, OVs are being explored for their capability to cure malignant glioma and other cancers with preclinical and clinical studies (Cloughesy et al., 2018).

Glioma Microenvironment

Different gliomas present with varying degrees of aggressiveness, histology, and genetic changes, making this category of primary brain neoplasms very diverse (Banerjee et al., 2021). The neural stem cells are involved in about 30% of the central nervous system tumors and they make up 80 % of malignant cases. These cells have the capacity to evolve into two types of cells: astrocytes or oligodendrocytes (Zong et al., 2015), or as direct neural stem cells. Glioma subtypes may now be distinguished as per the occupancy and pattern of genetic mutations in tumors of the brain and are associated with specific tumor histology and a WHO standard grade (Ceccarelli et al., 2016). Point mutations at arginine 132 (R132H) in isocitrate dehydrogenase 1 (IDH1) are often seen particularly diffuse low-grade gliomas (Delgado-López et al., 2017). The mutation occurs less often in anaplastic astrocytomas (WHO grade III) than it does in LGG-derived glioblastomas (secondary glioblastomas; WHO grade IV). The deletion of 1p/19q chromosomal regions allows for the classification of mutant IDH1 gliomas into two subtypes: mutant IDH1-1p/19q-codel and mutant

IDH1-non-codel (Banerjee et al., 2021). Genomic IDH1-1p/19q-codel gliomas are frequently observed in conjunction with oligodendrogliomas; on the other hand, mutant IDH1-non-codel gliomas are connected to oligoastrocytomas and astrocytomas, and they carry mutations in TP53, alpha-thalassemia, and X-linked mental retardation (Venteicher et al., 2017).

Gliomas can have complex signaling pathway issues arising from various genetic mutations. Growth factor receptor tyrosine kinases (RTKs) are among the most conspicuously disrupted signalling pathways in gliomas, partly as a result of platelet-derived growth factor (PDGF) and epidermal growth factor receptor overexpression (EGFR) (Nazarenko et al., 2012). There is evidence that activation of rat sarcoma (RAS), retinoblastoma/ Cyclin-dependent kinases (RB/CDK) N2A-p16 (INK4a), PTEN/PI3K/AKT, and TP53/MDM2/mouse double minute (MDM) 2/ MDM 4/CDKN2A-p14(ARF) pathways contribute to the growth of progression of glioma cells (Crespo et al., 2015). In addition, PI3K/ mTOR /AKT and ERK/MAPK molecular pathways have all been linked to NOTCH signaling activity, which in turn increases malignant aspects of WHO grade IV gliomas (Gersey et al., 2019). Paediatric gliomas may exhibit activation of the MAPK pathway or the associated downstream effectors as a result of *NF1 and BRAF* gene alterations. Those alternations are essential for carcinogenesis and proliferation in various malignancies (Mackay et al., 2017). Previous studies have shown the activation of Bone Morphogenic Protein (BMP) signaling in tumor cells originating from paediatric high-grade gliomas (HGG) (Mendez et al., 2020). About 20% of paediatric gliomas have somatic mutations in *Activin A receptor type I*; the gene responsible for encoding the type I BMP receptor (Oddrun Elise Olsen et al., 2014). It is important to focus on signaling pathway changes caused by particular genetic lesions in gliomas when developing novel targeted gene treatments.

Assessment of Tumor Microenvironment

Recent evidence indicates the tumor microenvironment as a factor in the regulation of antitumor immune responses (Qi et al., 2022). Typically, the CNS is referred to be an immune-privileged region because it exhibits reduced response to alloantigen exposure (Forrester et al., 2018). The immune privilege of the CNS is mainly attributed to the presence of the BBB and the lack of much lymphatic drainage in the brain. Specialized endothelial cells, astrocyte end-feet, and pericytes make up the BBB, making it a cellular barrier that is only partially permeable. Its primary role is to strictly control the transfer of ions, chemicals, and immune cells between the blood and the brain (Daneman & Prat, 2015). The immune response to the CNS antigens is limited because of a number of factors. These are for example, the deficiency of professional antigen-presenting cells within the CNS tissue, low expression of major histocompatibility complex (MHC) class I and II and no standard lymphatic drainage system in the CNS (Weller et al., 2008). Hence, CNS enables is a distinct site for tumor development and proliferation since effective anti-tumor responses require not only the generation of cancer-specific T cells but additionally the direct interaction of these T cells with the tumor antigens (Rocha Pinheiro et al., 2023). More recent evidence indicates that the CNS is not as immune-privileged as previously thought, but rather an immunological-distinct site that may initiate anticancer immune responses as well as immunotherapy (Louveau et al., 2015).

The majority of macrophages in the microenvironment of glioma tumors promotes tumor growth and inhibits the immune system. Up to a third of the tumor's bulk may be made up of TAMs (tumor-associated macrophages) (Roesch et al., 2018). Although there are two separate myeloid cell populations, microglial cells found in the brain, and bone marrow derived macrophages (BMDMs), share many characteristics, including immunoregulatory surface markers (Roesch et al., 2018). Myeloid-derived suppressor cells (MDSCs) are associated with both treatment resistance and glioma progression inside the tumor microenvironment (Ostrand-Rosenberg & Fenselau, 2018). GBM MDSCs have also been shown to exhibit high quantities of the protein PD-L1, which encourages T-cell exhaustion (Kumar et al., 2016). In the TME of GBM, many T lymphocytes show signs of exhaustion, such as decreased production of IL-2 and TNF-α. Exhausted T cells may display a high level of several "inhibitory" receptors including PD-1, CTLA-4, CD244, BTLA, CD160, Tim-3 and LAG-3 (Wherry & Kurachi, 2015). Gliomas have been linked to tumor growth and immune evasion, and this has been linked to the high frequency of T-regs present in gliomas. At present, therapeutic interventions address enhanced immune response against tumors by selectively targeting the conventional immune checkpoint pathways that contribute to the development of fatigued tumor-specific T cells. These pathways revolve around PD-1 to PD-L1 interactions and CD80/CD86 to CTLA4 signaling (Woroniecka et al., 2018).

Oncolytic Agents Targeting Glioma

OVs are naturally occurring or genetically modified recombinant viruses that may specifically target and kill tumor cells while mimicking their typical patterns of reproduction (Sweety Asija et al., 2023). Combining the improved knowledge of viral genome with advanced recombinant genetic engineering techniques made it possible to engineer an artificially attenuated and tumor selective replication competent virus (Liu et al., 2007). To enhance their tropism and achieve specific targeting of tumor cells, while minimising impact on non-neoplastic cells, OVs are genetically modified to identify tumor receptors while replicating under the control of oncogene promoters (Banerjee et al., 2021). The immunosuppressive conditions present in the tumor microenvironment were shown to boost the infectivity of OVs and promote increased oncolysis (Davola & Mossman, 2019). The

immune response mediated by viral- and tumor-specific T lymphocytes is crucial for the efficacy of oncolytic virotherapy, since it is triggered by the display of tumor epitopes by infected dying tumor cells (Li et al., 2016). Tumor-associated antigens (TAAs) are released by lysed tumor cells into the surrounding tissue, which the immune system may recognise. Activated immune cells are then mobilized and boost anti-tumor-immunity in the TME (Marelli et al., 2018).

Usually the healthy normal cells are not affected by the oncolytic viruses but conversely the cell lysis caused by the oncolytic virus in the glioblastoma helps the T cell activation (Figure 1). The tumor cell selectivity of OVs is aided by the downregulation of antiviral innate immune pathways in glioblastoma stem cells (Zhan et al., 2020). Malignant gliomas have shown significant responsiveness to therapy with OVs (Suryawanshi & Schulze, 2021), which, because to their isolated location surrounded by mitotically quiet normal neurons, have active cell cycles for their reproduction. OVT could turn immunologically "cold" TME of GBM into immunologically "hot" TME by causing inflammation and immunogenic cell death (ICD), increasing the expression of neoantigens, and recruitment of the tumor infiltrating lymphocytes (TILs) (Jafari et al., 2022). In many preclinical studies, OVs induced ICD along with cytotoxic T cell infiltration and reduced myeloid-derived suppressor cell (MDSC) accumulation (Carolien A.M. Koks et al., 2014). Evidence from clinical trials indicates that OVs may stimulate immunological responses against glioma, including infiltration by cytotoxic T cells and other important immune responses (Martikainen & Essand, 2019). It is crucial to rule out neurotoxic OVs when treating gliomas. With very few exceptions, these viruses fall into two general categories: neuro-attenuated viruses and non-neurotoxic viruses. Seneca Valley virus (SVV), parvovirus, myxoma virus, and M1 virus are examples of viruses that may not require further modification before being used in a therapeutic environment since they have not been shown to be neurotoxic (Zhang et al., 2016). Viruses having neurovirulent properties that have been altered by recombinant techniques to lessen neurotoxicity are known as neuro-attenuated viruses. Examples include the common cold virus, rotavirus, adenovirus, herpes simplex virus (HSV), varicella-zoster virus (VSV), poliovirus, and measles virus.

The third-generation oncolytic herpes simplex virus, G47Δ, which has been modified to include IL-12, proved the efficacy in increasing survival of glioma-bearing syngeneic mice when tested in a stem cell culture (Cheema et al., 2013)]. A phase II clinical trial of G47Δ was conducted with the patients who had GBM and received multiple intratumoral stereotactic injections of this virus along with temozolomide therapy (Todo, 2019). Also, the vectors of Newcastle disease virus (NDV) showed oncolytic and immunostimulatory effects which were beneficial (Schirrmacher et al., 2019). The LaSota strain of NDV, combined with temozolomide, considerably raised the apoptosis in glioma cells like no other combination therapy that could be done. Also it improved the survival rates in a rat xenograft tumor model together with this treatment. Moreover, the MV strains paired with anti-PD-L1 in vivo treatments were successful in raising the number of active CD8+ T cells inside tumours, thus extending survival in a mouse model of GBM (Hardcastle et al., 2016). There has been a thorough discussion of a variety of viruses, including their family classifications, genome sizes, immunogenicity, and blood-brain barrier (BBB) penetration capabilities (table 1). It is important to note that some viruses, like the Zika virus, Vaccinia virus, myxoma virus and parvovirus, are highly immunogenic and can traverse the blood-brain barrier, but other viruses, like the adenovirus and herpes simplex virus, is less immunogenic and cannot.

Essential features of OVs are listed in the below table.

Ongoing clinical trials involve viruses like AdV-tk, DNX-2401, G47Δ, Toca 511, DNX-2401 and PVSRIPO (table 2). They have been conducted in different phases, from Phase I to III. The delivery methods range from single injections to resection bed injections and adverse effects include symptoms like fatigue, headache, seizures, and more.

Anti-Cancer Mechanisms of OVs

Both direct and indirect oncolysis contribute to the OV's anticancer mechanism (Sweety Asija et al., 2023). In this approach, OVs preferentially infect and replicate inside cancer cells, triggering inflammation and cancer cell death via apoptosis or necrosis, and eliciting host immune responses due to exposure to tumor-associated antigens (TAA). In addition, bystander effects leading to vascular damage or immune modification within the tumor are indirect anti-neoplastic mechanisms that may be triggered (Russell et al., 2012). When the viral load in a tumor cell increases, it causes direct cell lysis, one of two forms of oncolysis. Tumor cells with high levels of infection emit damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), which then mobilize the host immune cells and target the cancer cell, causing cell death (figure 2).

Direct Oncolysis

Access of OVs to glioma cells is often mediated by multiple viral entry mechanisms. A rodent derived oncolytic H-1PV virus is the smallest (25nm) OV which can efficiently cross the BBB and reach the GBM TME. Many tumor cells have evolved to express receptors for OVs attachment. Some tumor cells display overexpressed CD46 and CD155 proteins on their cell surfaces which are used by some viruses such as Polio and MV for primary attachment and entry (Anderson et al., 2004). Furthermore, the formation of OVs is strongly stimulated by the ongoing metabolism of cells in the tumor. Moreover, tumor cells' disrupted innate defense signaling pathways provide the ideal conditions for additional viral replication and growth. Reovirus is one kind of virus that interacts

with the protein kinase R pathway. This virus specifically targets tumours that show upregulation of the *Ras* pathway attributed to its unusual double-stranded RNA genome (Nishikawa et al., 1994).

In order to significantly improve OV's tropism, it is possible to genetically modify it in a number of ways. Tumor-suppressor gene inactivation can be used to increase targeted infection of tumor cells by manipulating certain genes, such as altering or eliminating them. This approach aims to impair the ability of the OVs to replicate in normal cells and mediate more tumor selective replication (Qi et al., 2022). The oncolytic adenovirus (oAd) oncorine, characterised by the absence of E1B-55 kDa, often has limited replication capacity in normal cells. Conversely, it exhibits a preference for replication in tumor cells that exhibit a deficiency in this particular protein p53 (Fong et al., 2014). In addition, the tumor-specific promoters allow the inclusion of genes that are vital for the growth of OVs in TME, thus enhancing the specificity of OV targeting tumors (Qi et al., 2022). Tissue specific promoters that drive the E1A expression in enhancing oAd targeting, may include hypoxia response promoter (HRE), human telomerase reverse transcriptase promoter (hTERT), mucin 1 promoter (DF3/MUC1), alpha-feto protein promoter (AFP) and prostate-specific antigen promoter (PSA) (Tian et al., 2022). One method to improve the precision of tumor targeting is to modify viral capsid proteins for tropism (Qi et al., 2022). Viral capsid protein fiber exchanges or the creation of fiber chimaeras by the swapping of knob domains and axons can alter adenovirus tropism (Jiang et al., 2006). Human glioblastoma and other tumor cells significantly express EGFR and HER2, which have been effectively retargeted using genetically altered OVs (Gambini et al., 2012). OVs may directly lyse tumor cells after specifically targeting them and releasing progeny of infectious OVs without harming neighboring healthy cells. Recent research showed an interesting mechanism for the abscopal effect of OVs, in which tumor derived extracellular vesicles carries OVs from primary injection site to a distant metastatic site where they showed direct oncolysis on the metastatic tumors, a mechanism completely different from immune activation (Yoshihiko Kakiuchi et al., 2021).

Indirect Oncolysis

By attracting immune cells that are essential for reducing tumor burden, OVs have the ability to transform immunologically inactive "cold" tumors into immunologically active "hot" tumors, improving the responsiveness of immunotherapeutic approaches. The beginning of the lytic cycle of OVs can result in a number of consequences, for example, the liberation of tumor-associated antigens (TAAs), changing the TME and destroying the extracellular matrix. The target host's innate and adaptive immune responses subsequently get activated just after the lytic cycle (Sweety Asija et al., 2023). The first reaction of the innate immune system is to activate cells such as natural killer cells, granulocytes, neutrophils and antigen-presenting cells. This activation happens because of the recognition of pathogen-associated molecular patterns (PAMPs) and toll-like receptors (TLRs), both of which are essential for this purpose (Sweety Asija et al., 2023). Dendritic cells armed with TAAs as well make the adaptive immune system to start working. The tumor-specific antigens are also released and this makes it easier for T lymphocytes to infiltrate the tumor. The removal of damage-associated molecular patterns that are the result of necrotic process induced by OVs is able to activate dendritic cells and thus, cause acquired immune responses.

To elicit the anti-tumor response, OVs must initially modulate the immunosuppressive tumor microenvironment, induce tumor cell lysis, facilitate the presentation of TAAs to dendritic cells, and promote the migration and viability of effector T cells within the tumor site (Gujar et al., 2018). In order to augment immune responses, particularly in tumors that exhibit low immunogenicity, the oncolytic virus (OV) employs diverse strategies to disrupt the immunosuppressive milieu. This is accomplished by equipping itself with immune-modulating agents, such as TAAs, targets for CAR T cells, and immunological checkpoint inhibitors. It is possible to modify OVs to express immune modulatory molecules with the goal of harming tumor cells and interfering with the milieu that promotes tumor growth (Sweety Asija et al., 2023).

Tumor blood vessels may be damaged by OVs, which might reduce or even stop blood supply to the tumor and cause hypoxia and nutritional deficiencies (Breitbach et al., 2013). Massive cell death is caused by the direct contact of OV with TME blood vessels, particularly the neo vasculature. The ensuing tumor death is characterised by irreversible damage to the tumor vasculature brought on by the neutrophil-induced formation of microthrombi in blood vessels along with fibrin accumulation (Sweety Asija et al., 2023). Clot development results in significant cell death that is confined to the TME. Previous study showed the function of intravascular clot formation in the onset of strong antitumor effectiveness via tumor cell death and with a reduced rate of cancer cell proliferation (Sweety Asija et al., 2023). OV infected endothelial cells release chemokines which allows immune cells to cross the BBB. OVs can effectively participate in anti-glioma activity and be a component of highly combinatorial anti-glioma therapies since several anti-tumor pathways cooperates (Sweety Asija et al., 2023).

Challenges of Glioma Virotherapy

Surpassing the BBB

OVs must overcome a number of challenges to reach the TME, which includes host defense mechanism by complement factors and/or neutralizing antibodies, as well as antiviral immune cell responses such as virus specific CD8 T lymphocytes (Suryawanshi & Schulze, 2021). The appropriate viral load that needs to reach TME is reduced due to the non-specific absorption of a portion OVs in several organs, such as the spleen, liver, lung and tissue-resident macrophages. Moreover, physical barriers prevent virus particles

from travelling from vascular to extravascular compartments; one such physical barrier that is particularly strong is the BBB (Suryawanshi & Schulze, 2021). A complex system of intricately interconnected cells, including endothelial cells, pericytes, microglia and astrocytes, makes up the architecture of the microvasculature of the CNS (Suryawanshi & Schulze, 2021). The BBB regulates the transport of chemicals, ions, and cells across the blood vessel membrane and into the brain in order to maintain homeostasis and ensure that neurons are functioning at their best. Even though, the BBB plays an essential in preventing inflammation, toxicity, and damage to the brain (Daneman & Prat, 2015). However, it also represents a significant barrier to the delivery of systemic therapies to the tumors found in the CNS compartment, excluding some OVs.

Certain viruses, such as Semliki Forest virus (Ramachandran et al., 2017), vaccinia virus, chimeric vesicular stomatitis virus (VSV) (Muik et al., 2014), parvovirus H-1 (Karsten Geletneky et al., 2010), Mengovirus (Ruiz et al., 2016) and Seneca Valley virus-001(Liu et al., 2013), have shown the capacity to effectively penetrate the BBB in order to access and infect tumors in animal models. Additionally, clinical evidence has demonstrated that intravenously administered oncolytic parvovirus H-1 can penetrate malignant glioma tumors in glioma patients (Geletneky et al., 2017). A replication controllable OV has been engineered in response to concerns about uncontrolled viral replication, which has made OVs potential candidate of anti-tumor therapy (Islam et al., 2020). Because of their reduced size, innate affinity for neural tissue, or capacity to employ host immune cells as carriers, certain OVs, such oncolytic AAV (25 nm), have been reported to spontaneously cross the BBB to infect and destroy tumor cells in the CNS compartment. While endovascular selective intra-arterial administration (ESIA) and local convection-enhanced delivery (CED) may be able to maximise the movement of OVs by tumor cells, carrier cells provide a viable option that may aid in improving the delivery of OVs across the BBB (Suryawanshi & Schulze, 2021).

Tumor Extracellular Matrix (ECM)

In solid tumors other than glioma, ECM has been shown to block the therapeutic benefits of chemotherapy and radiation. Previous preclinical research has demonstrated that the basic physical mechanism preventing OVs from dispersing intratumorally, such as increased production of extracellular matrix (ECM) components like collagen and hyaluronic acid (HA), causes a marked rise in interstitial fluid pressure within the tumor mass (Wojton & Kaur, 2010). Another study has shown that glioma cell production of extracellular matrix substances such HA, fibronectin, thrombospondin, and tenascin-C is enhanced, that is also responsible for the ECM physical impediment of OVs (Khoonkari et al., 2022). Conversely, elevated levels of ECM components may cause the tumor to become less receptive to chemotherapy and radiation therapy by reducing its availability of nutrients and oxygen and causing tumor hypoxia and metabolic stress, respectively. Additionally, ECM elements, especially collagens, promote immunological entrapment by preventing T cell migration, resulting in the exclusion of effector immune cells and thus a malfunction of immune surveillance. When compared to tumor sites with low levels of HA, T cell infiltration was observed to be lower in HA-rich tumor locations in both human and mouse glioma (Juri Kiyokawa et al., 2021). Although, as previously mentioned, the targeting the ECM by OVs may boost intratumoral dispersion of the virus Qi et al. (2022).

Recommendation & Future Directions

Combination Immunotherapy

Immunotherapy for cancer employs the patient's own inherent and adaptive defence mechanisms to target and eliminate malignant growths. Although immunotherapy has become standard practice for treating several types of cancer, its effectiveness in the treatment of glioma remains unsatisfactory (Qi et al., 2022). Immune checkpoint inhibitor (ICI) monotherapy has shown only a modest ability to treat disease in preclinical and clinical studies, and the combination of anti-PD-1 and anti-CTLA-4 treatment has moreover demonstrated substantial adverse effects in clinical trials, despite promising preclinical trial outcomes (Omuro et al., 2017). CAR-T cell treatment and immunization techniques are now undergoing clinical studies, although the outcomes so far have been disappointing. The presence of immune cells and silencing or blocking of immune suppressive markers in the TME is required. Tumors with minimal TIL infiltration are often less immune-therapeutically receptive (Topalian et al., 2016). Therefore, the immunosuppressive GBM TME, which includes immunosuppressive immune cells, tumor cell-derived inhibitory cytokines and PD-L1 on tumor cells have become the primary contributing factors of the reduced effectiveness of immunotherapies in glioma, particularly for CAR T cells (Qi et al., 2022).

Previous studies showed that ICI combination with OVs enhanced therapeutic efficacy and safety in various cancer models. One way in which OVs might enhance overall efficacy of ICI in glioma with limited T-cell infiltration is by recruiting tumor specific T cells to stimulate an anticancer immune response. In contrast, the responsiveness of glioma cells to ICIs is augmented by the induction of PD-1 expression on T cells and PD-L1 expression on tumor cells, which is facilitated by OVs via the initiation of an inflammatory immune reaction. Multiple preclinical studies have shown that the combination of ICI with OV's has significant therapeutic potential. In GL261/CT2A tumor bearing orthotopic mouse models, ZIKV, reovirus, MV and VSV (respectively armed with HIF-2, c-Myc, Sox-10, and tyrosinase-related protein 1) indicate better therapeutic outcomes than monotherapy (Juri Kiyokawa et al., 2021). The

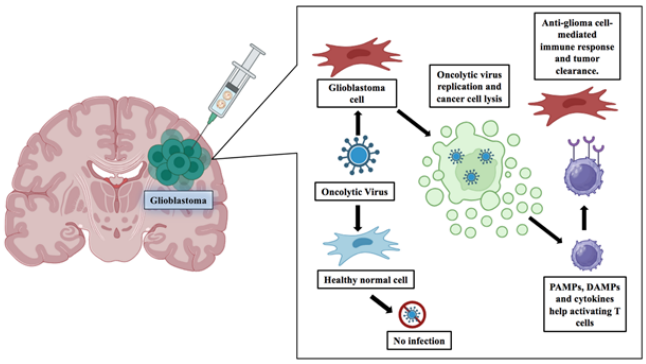

Figure 1. OVs in addressing glioma.

Table 1. Essential features of OVs.

Virus Type	Family	Genome Size	Viral Immunogenicity	BBB Penetration	Reference
Adenovirus	Adenoviridae	32kb	Low	No	(Kaufman et al., 2016)
Parvovirus	Parvoviridae	5kb	High	Yes	(Kaufman et al., 2016)
Herpes Simplex Virus	Herpesviridae	152kb	Low	No	(Kaufman et al., 2016)
Retrovirus	Retroviridae	7-10kb	Low	Yes	(Lundstrom, 2019)
Vaccinia virus	Poxviridae	190kb	High	No	(Bommareddy et al., 2018)
M1 virus	Togaviridae	11.7kb	Moderate	Yes	(Lundstrom, 2019)
Measles virus	Paramyxoviridae	16kb	Moderate	No	(Lundstrom, 2019)
Zika virus	Flaviviridae	10.7kb	High	Yes	(Lundstrom, 2019)
Myxoma virus	Poxviridae	161.8kb	High	No	(Bommareddy et al., 2018)
Newcastle disease virus	Paramyxoviridae	15kb	Low	Yes	(Lundstrom, 2019)

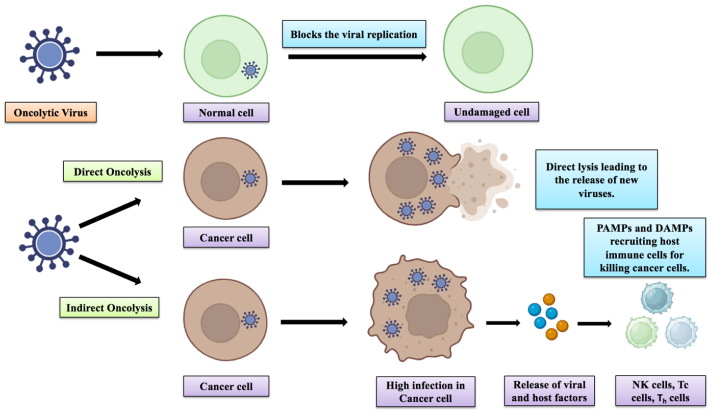

Figure 2. Direct and indirect cancer oncolysis by OV.

Table 2. OVs in different clinical trials

Virus	Clinical trial number	Phase	Status	Delivery	Median OS	Adverse impact	Reference
AdV-*tk* + VCV	NCT00589875	IIa	Completed	Resection Bed	16.7*	Fatigue, fever, headache, wound complication, seizure	(Wheeler et al., 2016)
AdV-*tk* + GCV	N/A	I	Completed	Single IT injection.	16.8*	Seizure, hemiparesis, thrombocytopenia,hyponatremi, confusion, lethargy	(Trask et al., 2000)
AdV-*tk* + GCV	NCT00870181	II	Completed	Intra-arterial cerebral infusion	10.4*	Nausea/vomiting, vasospasm, transaminitis	(Ji et al., 2015)
DNX-2401	NCT00805376	I	Completed	Single IT injection. (Arm A), Single IT injection + resection bed injection (Arm B)	9.8*	Headache, speech disorder, hemiparesis, convulsion, muscular weakness, visual field defect	(Lang et al., 2018)
DNX-2401 + IFN-γ	NCT02197169	Ib	Completed	Single IT injection	Not published (OS 12 m of 33%, 18 m of 22%)	Fatigue, headache, seizures	(Lang et al., 2017)
G47Δ	UMIN000002661	I/II	Completed	IT injection, 2 doses	30.5 (7.3‡)	Headache, fever, vomiting, leukopenia, CN disorder, seizure	(Todo et al., 2022)
Toca 511 + Toca FC	NCT01470794	I	Completed	Resection bed injection, Toca FC oral	11.9	Rash, mucositis, facial swelling, hemorrhagic enteritis, colitis, nausea, vomiting, diarrhea	(Cloughesy et al., 2018)
PVSRIPO	NCT01491893	I	Completed	IT CED	12.5	Fatigue, gait disturbance, confusion, dysphagia, headache, paresthesia, pyramidal tract syndrome, seizure	(Desjardins et al., 2018)
NSC loaded with CRAdSurvivin-pk7	NCT03072134	I	Completed	Resection bed injection.	18.4	Meningitis, thromboembolic event, encephalopathy, cerebral edema, muscle weakness	(Fares et al., 2021)
AdV-*tk* + VCV	NCT03576612	I	Active, not recruiting	Resection Bed	-	-	-
PVSRIPO	NCT02986178	II	Active, recruiting	IT CED	-	-	-
rQNestin34.5v.2 (CAN-3110)	NCT03152318		Active, recruiting	Single IT injection.	13.25	Not published	(E. Antonio Chiocca et al., 2021)
Toca 511 + Toca FC	NCT02414165	II/III	Terminated	Resection bed injection, Toca FC oral	11.1	Aphasia, hemiparesis, headache, seizure	(Cloughesy et al., 2020)
Toca 511 + Toca FC	NCT02598011	Ib	Withdrawn	Resection bed injection, Toca FC ora	-	-	-
Toca 511 + Toca FC	NCT04105374	II/III	Withdrawn	Intra-cranial injection	-	-	-
PVSRIPO	NCT04599647	Expanded access	No longer available	IT CED	-	-	-

efficacy of oncolytic adenovirus Delta-24-RGDOX in combination with anti-PD-L1 is also shows enhanced efficacy (Jiang et al., 2017). Additionally, the combination of G47Δ-mIL12, and anti-CTLA-4 and anti-PD-1 reduced the clinical toxicity and showed robust anti-tumor immunity (Saha et al., 2017). In case of adoptive T-cell (ACT) therapy, donor T cells must reach the tumor, and remain there for effective antitumor response. Therefore, by controlling the local TME, OVs may more effectively increase the response of ACT to glioma treatment. OVs have the potential to address the challenges encountered by ACTs via their ability to modulate the immunosuppressive TME and recruit substantial influx of ACTs to the tumor sites. Furthermore, the selective eradication of tumor cells by OVs results in the release of PAMPs and TAAs improves the functionality of effector T cells. By arming additional therapeutic genes into OVs genome, effectiveness of ACT is enhanced. For example, oncolytic adenovirus armed with IL-7significantly increased the effectiveness of B7H3-CAR-T in glioma tumor model (Huang et al., 2021). A preclinical study by Nishio and Dotti (2015) found that the survival rate of mice with neuroblastoma was extended by CAR-T therapy with Ad5Δ24 equipped with the immunomodulatory molecules IL-15 and chemokine CCL5 receptor.

Combination Chemotherapy

At present, the primary pharmacological intervention for glioma treatment is temozolomide (TMZ), an orally administered prodrug with alkylating properties. Following TMZ treatment, DNA becomes methylated (alkylated) resulting in cell damage and apoptosis. Even though the addition of TMZ to conventional therapy was initially considered as an effective treatment option for glioma, it only increased patients' median survival as compared to placebo by not even three months (Stupp et al., 2005). A significant clinical issue that has not yet been resolved is the tumor resistance to alkylation agents caused by the O^6-methylguanine-DNA methyltransferase (MGMT) DNA repair mechanism (Hegi et al., 2005). Recent preclinical research indicates the OVs mechanism for overcoming the TMZ resistance to glioma tumor. For instance, A modified form of the herpes simplex virus called OHSV-TRAIL is able to specifically target and initiate cell death processes in glioblastoma stem cells that are resistant to the chemotherapeutic medication temozolomide. This is accomplished by tampering with certain signaling pathways associated with DNA damage response and cell death. This strategy has been proven in mouse experiments to increase the survival rates of animals harbouring these hardy tumor cells (Jahan et al., 2017). Furthermore, when coupled with TMZ, NDV demonstrated an improved synergistic antitumor impact by inhibiting the Akt signalling pathway and activating AMPK. Moreover, TMZ exerts impacts on the immune system in addition to the typical direct anticancer effects. Oncolytic adenovirus DNX-2401 and TMZ combination therapy regimen for glioma was shown to increase the ability of CD8+ T cells to recognize tumor cells (Jahan et al., 2017).

Conclusion

OVs have evolved to develop a variety of tumor-killing methods. In order to improve safety, tumor-specific replication, along with immune stimulation through incorporation of various genes by recombinant DNA techniques, there has been growing acceptance of their potential for anticancer therapies. Delivery to the glioma TME can be achieved by the deployment of viruses with the capacity to traverse the BBB, and/or through direct injection of the virus into the tumor site. A number of clinical studies have indicated the potential effectiveness of OVs in the treatment of gliomas. OV, a unique immunotherapeutic approach not only selectively target gliomas but also activates the body's potent anti-tumor immunity, which may work in combination with other immunotherapeutic drugs to enhance their effectiveness. Preclinical and clinical settings are being used to investigate this type of treatment, which involves monotherapy or additional treatments in combination. In several clinical investigations, these combinatorial tactics are being investigated in an effort to increase high-grade glioma patient survival. Further studies are required to determine the appropriate virus strain, dose selection, mode of administration as well as optimum schedule during selection mono or combination therapy. In summary, glioma targeting OV shows promising potential and could be a part of anticancer regimens in the near future.

Author contributions

A.T., S.S.S., and S.M.B.U.I. conceived and designed the analysis. A.T. and N.J. collected the data. A.T., N.J., M.F., J.S.J., N.B., S.S.S., and S.M.B.U.I. wrote the paper. S.S.S. and S.M.B.U.I. revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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