Review

ANNALS OF MEDICINE & SURGERY

OPEN

Synergistic effects of herpes oncolytic virus and cyclophosphamide for recurrent malignant glioma: a narrative review

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Abstract

Gliomas, comprising nearly 80% of brain malignancies, present a formidable challenge with glioblastomas being the most aggressive subtype. Despite multidisciplinary care, including surgery and chemoradiotherapy, the prognosis remains grim, emphasizing the need for innovative treatment strategies. The blood-brain barrier complicates drug access, and the diverse histopathology hinders targeted therapies. Oncolytic herpes viruses (oHSVs), particularly HSV1716, G207, and rQNestin34.5v, show promise in glioma treatment by selectively replicating in tumor cells. Preclinical and clinical studies demonstrate the safety and efficacy of oHSVs, with T-Vec being FDA-approved. However, challenges like viral delivery limitations and antiviral responses persist. The combination of oHSVs and combining cyclophosphamide (CPA) addresses these challenges, demonstrating increased transgene expression and viral activity. The immunosuppressive properties of CPA, particularly in metronomic schedules, enhance oHSV efficacy, supporting the development of this combination for recurrent malignant gliomas. CPA with oHSVs enhances viral oncolysis and extends survival. CPA's immunomodulatory effects, suppressing regulatory T cells, improve oHSV efficiency. While obstacles remain, this synergistic approach offers hope for improved outcomes, necessitating further research and clinical validation.

Keywords: cyclophosphamide, glioma, herpes, neuro oncology, oncolytic virus

Introduction

Gliomas are the most common central nervous system malignant neoplasms. Astonishingly diverse, these tumors account for nearly 80% of all brain malignancies. Among them, ~50% of gliomas are glioblastomas, which are not only the most prevalent subtype but also the most aggressive—killing nearly a quarter of a million people each year[1,2]. Gliomas are primary brain tumors driven from neuroglial progenitor cells, which have been histologically classified into astrocytic, oligodendroglial, and ependymal. They are also divided based on two key genetic derangements: IDH mutations and 1p/19q co-deletion. IDH mutant and 1p/19q co-deletion tumors have the best prognosis, IDH mutant but 1p/19q non-co-deleted tumors have intermediate prognosis, while IDH-wild-type tumors are associated with poor diagnosis[3].

The unmitigated threat of mortality due to tumor progression looms large over the vast majority of patients, despite provisions of optimum multidisciplinary care that include but are not limited to maximum cytoreductive surgery plus concomitant adjuvant chemoradiotherapy. With a dismal 2-year survival rate averaging 30% and a median survival of less than one and a half years from initial diagnosis, treatment remains challenging and elusive[4,5]. The 5-year survival rate for glioblastomas is 5% in spite of optimum treatment. As such, not only are the present treatment options for gliomas limited and associated with adverse side effects, they provide a less than promising survival benefit. Anatomical considerations often limit the degree of tumor resection and complete removal is hindered due to infiltration of surrounding structures[6–8]. Preoperative evaluation usually includes an array of hematological tests, in addition to liver and kidney assessments to establish a baseline and assess the patient's fitness for chemotherapy. Abandonment, interruptions and postponement of treatment is not uncommon. Whereas regular monitoring of liver function is needed for patients receiving temozolomide, nitroureas such as carmustine, nimustine, lomustine and fotemustine can also result in cumulative derangements in white cell and platelet function[9]. Although

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:5354–5360

Received 15 June 2024; Accepted 6 July 2024

Published online 17 July 2024

http://dx.doi.org/10.1097/MS9.0000000000002384

highly advanced conformal radiotherapy may improve accuracy in targeting malignant tissue while sparing healthy brain matter, several neurological structures including the retinae, optic nerves, optic chiasm and deeper structures like the pituitary gland, brainstem and hippocampus are often at an elevated risk and must be protected. In addition to heavy-ion radiotherapy, randomized trials are required to assess whether proton-beam therapy is a better option than conventional radiotherapy for patients at risk of toxicities despite favorable prognosis[10,11]. A seemingly insurmountable challenge is the histopathological diversity amongst gliomas and, as a result, there are no targeted therapies currently approved for their treatment[12].

Another formidable challenge that the glioblastoma treatment faces is due to the blood-brain barrier's (BBB) role in limiting drug access to the brain, the complex blood-tumor barrier, and the tumor's interactions with the brain. The BBB in glioblastoma becomes leaky due to downregulated tight junctions and upregulated transporter proteins, allowing tumor-promoting substances while blocking therapeutic agents. Approaches like hyperosmotic therapy and convection-enhanced delivery have shown limited success, with issues such as technical challenges and rapid drug transit. Magnetic resonance-guided focused ultrasound (MRgFUS) is promising for disrupting the BBB, but challenges remain. Surgical implantation of drug delivery devices is explored but it faces concerns. Glioblastoma's invasive nature utilizes tumor microtubes (TMs) to resist therapy and drive recurrence. Innovative strategies are needed to improve treatment outcomes[13].

No review article in the literature exclusively discusses the role of cyclophosphamide in the treatment of glioma and its synergistic effect with herpes oncolytic virus. In this narrative review, we will examine the clinical and preclinical synergistic effects of oncolytic viruses particularly rQNestin34.5v.2 and cyclophosphamide for the treatment of recurrent malignant gliomas, in the light of current literature.

Herpes oncolytic viruses as a therapy for gliomas

Overview and mechanism of action

First reported in 1991, the use of oncolytic viruses (OVs) is a novel treatment in glioma therapeutics, with the oncolytic herpes simplex virus (oHSV) having seen the furthest progress in the clinical domain[14–19]. Genomic stability and feasible engineering coupled with potent cytolytic power render oHSV an interesting and appealing weapon against malignant gliomas. Moreover, in event of adverse reactions, the abundance of anti-herpetic drugs also provides assurance[20]. The mechanism of action of oHSVs is straightforward and involves immunogenic cell death. The virus selectively replicates inside tumor cells leading to their destruction. An additional pathway integral to its cytolytic capabilities in an in-situ vaccine effect that involves the stimulation of anti-tumor immunity[21,22]. Early trials with HSV1716 demonstrated no evidence of HSV-mediated adverse events or toxicities[23–25].

Types of herpes oncolytic viruses

As an emerging glioma treatment, over half a dozen oHSVs are currently being or have been tested in published clinical trials with or without other anti-cancer agents. The oHSVs include HSV1716, G207, HF10, NV1020, rQNestin34.5v, G47Δ, M032, C134 and talimogene laherparepvec (T-Vec). The latter is presently the most extensively investigated oHSV and achieved FDA approval following a trial that involved advanced melanomas back in 2015. On the basis of their structure, these viruses can be divided into three categories that is unarmed, re-targeted and armed. Unarmed oncolytic viruses are genetically altered but lack a transgene for example G47Δ are constructed from G207 by removing the ICP47 gene. The re-targeted class includes viruses that are genetically modified for tumor receptor-specific viral entry. The armed oHSVs are developed to express therapeutic transgene variants. Nevertheless, the anti-tumor efficacy of oHSV therapy is limited by either existing or potential pitfalls such as inadequate viral delivery, inefficient viral entry, limited replication and/or dissemination in the tumor microenvironment (TME) or due to the antiviral response within the host[26–30].

Preclinical studies, clinical trials and outcomes

In the first study involving recurrent high-grade gliomas (HGG), four out of nine patients went on to live beyond 14–24 months after being treated with replication-competent HSV1716 stereotactic injections of 103–105 plaque-forming units per ml. Moreover, no evidence of viral reactivation or shedding was observed[24]. In another study that confirmed the safety and replication of the same oHSV subtype, intratumoral injections among 12 HGG patients were followed by tumor resection 4–9 days later. Among two patients, Infectious HSV was recovered from injected sites and viral DNA was further detected in 10 patients at the primary site and in 4 patients at the distal tumor site[25]. In the third study, maximal surgical resection was first carried out among 12 recurrent or newly diagnosed HGG patients followed by cavity-site injections of HSV1716 (105 pfu). For 15–22 months following treatment, three patients were found to be clinically stable. A demonstrable radiographic reduction of the residual tumor was observed over a period of 22 months with seroconversion in two of three seronegative patients[23].

Although the safety and efficacy of the G207 oHSV has been reported preclinically[31], several Phase I/Ib clinical studies among patients with malignant glioma or recurrent GBM either are available. Involving nearly double the patients as each individual trial, the first study among recurrent HGG patients received an intratumoral injection of G207 (109 pfu) at five sites for about three doses. Four patients survived 7–19 months and no virus shedding was observed[32]. Next, a Phase Ib trial was initiated in six recurrent cases who received two doses of G207 totaling 1.15 × 109 pfu, with 13% of this dose injected stereotactically into the tumor, followed by en bloc tumor resection and administration of the remaining virus dose at multiple sites into the resected cavity wall. Replication and anti-tumor activity (i.e. radiographic and neuropathologic response) of G207 were reported[33]. Furthermore, a Phase I clinical trial involved a combination of G207 with radiotherapy. Nine progressive recurrent malignant glioma patients (seven of them bearing GBMs) were stereotactically/intratumorally treated with G207 (1 × 109 pfu) 24 h prior to single focal 5 Gy radiation. The combination therapy was well tolerated and no patients developed HSV-related encephalitis. Three instances of marked radiographic response to treatment were observed[29]. A long-term response (6 years disease free-survival) was noted in a case study by Markert and colleagues in which stereotactic G207 injections with minimal adjunctive chemotherapy were used[34].

Phase I–IIa clinical trials among 21 patients with residual or recurrent GBM have demonstrated the tolerability, anti-tumor efficacy and safety of the unarmed G47Δ. Stereotactic injections of the oHSV were carried out twice in 2 weeks followed by every 4 weeks for a total of 6 times[35]. Other oHSV like the M032 virus, which have demonstrable safety are being clinically tested in patients with recurrent GBM[36].

Cyclophosphamide as a therapy for gliomas

Overview and mechanism of action

Cyclophosphamide (CPA) boasts of wide-ranging applications as an alkylating agent that is commonly used for the treatment of hematologic and solid malignancies. It has significant immune-modulatory activities, most notably its ability to suppress regulatory T cells and thereby counteract immunosuppression in the tumor microenvironment[37]. In the presence of cyclophosphamide, the efficiency of oHSVs is demonstrably improved. CPA decreases the infiltration of peripheral blood mononuclear cells (PBMC) and enhances the production of IFN-γ by natural killer (NK) cells. Pre-administering cyclophosphamide acts by hindering viral clearance and enhancing replication within tumor cells due to its immunosuppressive effect[38].

Innate immunity plays an important role in controlling viral infections[39–41]. In a recent study, Fulci and colleagues have demonstrated that the use of cyclophosphamide to inhibit the host innate immune response helps promote oHSV replication in brain tumors, thus augmenting its anti-tumor effects. Additionally, the oHSV-mediated proliferation of mononuclear cells in brain tissue is reversed[38,42,43]. Interferon α/β receptor 1 (IFNAR1) -dependent proliferation of dendritic cells is stimulated by cyclophosphamide in animal studies. It is believed that immune cell infiltration is promoted by IFNAR1 signaling and also plays a part in the control of metastatic tumor progression. The combined action of cyclophosphamide with type-1 interferons helps in systemic dendritic cell reactivation and induction of tumor cell apoptosis[44,45].

Current use in glioma therapy

As demonstrated in various studies, the immunosuppressive effects of CPA are most appreciable when it is administered on a modified, metronomic schedule, called as medium-dose, intermittent chemotherapy (MEDIC)[46–50]. A study in large brain tumor xenografts by Doloff and colleagues showed that the immune response following cyclophosphamide use in a recurring 6-day metronomic schedule is associated with tumor regression and ablation. Furthermore, it was demonstrated that rather than antiangiogenesis, it was anti-tumor innate immunity that acted as the primary mechanism that drove the changes observed in these grafts[47].

Vital to drug-stimulated anti-tumor immune response is the extensive transcriptional change observed following MEDIC cyclophosphamide treatment[51,52]. In a study by Fulci and colleagues on immunocompetent rats, comparisons were made between the expression of LacZ genes and ICP4 (infected-cell protein 4) genes in tumor cells with and without CPA pretreatment. This was done at about 6 h and then three days following treatment with HSV. Irrespective of CPA use, at about 6 h after oHSV delivery, ~50% of tumor cells showed viral-mediated gene expression. In the absence of CPA, however, below 10% of tumor cells exhibited viral-mediated gene expression at three days, in contrast to 80% of tumor cells showing oHSV-mediated gene expression following CPA pre-administration[38].

Several other studies have demonstrated that not only CPA enhances viral oncolysis of tumor cells, but it also helps prolong the survival of animals[42,53,54]. Another notable benefit of using CPA is the reduction in the dose of oHSV that is observed with CPA use[55]. Moreover, the risk of drug toxicity due to CPA is minimized as metronomic schedules overcome the requirement for extended periods of recovery between each successive cycle[56].

CPA is commonly utilized in experimental research on wild-type HSV pathogenesis and is known to facilitate the spread of wild-type HSV1 within the central nervous system (CNS) from systemic sites[57]. This effect has traditionally been attributed to CPA's myelosuppressive properties, although the molecular mechanisms underlying this phenomenon have not been

extensively explored. Notably, CPA has been linked to a reduction in inducible nitric oxide synthase iNOS production in alveolar macrophages in response to mycoplasma infection[58].

Effect of combination of cyclophosphamide and oncolytic herpes viruses on enhanced Viral-mediated transgene expression

In an immunocompetent rat model, a study was conducted to investigate the impact of CPA on viral-mediated transgene expression using oncolytic herpes simplex viruses (hrR3 and MGH1). CPA was administered either simultaneously with a viral injection or 2 days before. The results of the study observed that CPA substantially increased the anatomical extent of lacZ transgene expression within tumors in comparison to the control group. Notably, pretreatment with CPA demonstrated even higher levels of transgene distribution within tumors compared to simultaneous treatment. Furthermore, these positive effects were not limited to hrR3 but were also observed with MGH1, suggesting that the findings could be generalized to different strains of oncolytic HSV. Tumor explant assays revealed that CPA promoted the survival of the oncolytic virus within infected tumors. This effect prevented the significant drop in virus titers that were observed in control tumors, demonstrating the ability of CPA to sustain viral activity within the tumor microenvironment[54]. In terms of animal survival, rats treated with both CPA and hrR3 exhibited a significant prolongation of survival when compared to rats treated with hrR3 alone or CPA alone. This was particularly remarkable given the aggressive nature of the D74HveC tumor cells, emphasizing the potential of the CPA and oncolytic HSV combination in enhancing the therapeutic efficacy against aggressive brain tumors in rat models. In previous studies, OV administration in athymic rat models led to complement activation, even without neutralizing immunity. Interestingly, different species activated the complement system through various pathways, with rats and humans using the classical pathway and mice (and rats) using the lectin or mannose-binding protein pathway. Inhibiting complement activation using cobra venom factor (CVF) or CPA enhanced initial tumor infection by intravascular OV[43]. While carotid artery injection of 109 PFUs of OV was possible, only 0–4 PFUs initially infected brain tumors without complement inhibition. However, approximately 30–50 PFUs were measured when complement

inhibition was applied. Complement depletion with CVF alone increased initial tumor infection but didn't enhance subsequent rounds of viral propagation. Interestingly, CPA, unlike CVF, not only inhibited complement but also acted on additional pathways within tumors. CPA's action was associated with a rapid decrease in PBMC counts and suppression of antiviral cytokine genes. This suggested that CPA modified the tumor's permittivity for OV propagation, likely by reducing PBMC concentration and suppressing their production of antiviral cytokines[59].

Role of antiviral cytokines and their mRNA expression against oncolytic viruses

Antiviral cytokines and their mediators play a role in modulating HSV replication in the nervous system. IFN-γ, primarily produced by extrathymic γ/δ TCR + T cells, synergizes with TNF-α, primarily from macrophages, to inhibit HSV replication by stimulating iNOS production and activating 2′-5′-oligoadenylate synthetase (OAS), leading to cellular inhibition of viral replication[60]. Interferons α/β are potent antiviral cytokines that confer cells with resistance to productive HSV infection and replication by inducing OAS and protein kinase R (PKR). Notably, PKR activation is linked to the proinflammatory NF-κB pathway and iNOS production in response to influenza virus. The role of interferon-γ in limiting HSV infection is debated, with varying opinions on its significance. It is primarily produced by activated macrophages and extrathymic γδ-TCR + T cells in response to viral infections. IFN-γ can directly hinder HSV replication and promote iNOS production, a potent inhibitor of HSV replication[61]. Interleukin-15 and -18 are intriguing cytokines. In humans, IL-15, produced by activated PBMCs, plays a role in activating NK cells against HSV1. IL-18, produced by activated macrophages, induces IFN-γ production by mouse helper T cells and NK cells. Additionally, TNF-α serves as an important mediator in the initial inflammatory response, and inhibiting its expression appears necessary for efficient viral infection and replication. In addition to the cytokines examined, CPA likely affects the expression of various other mediators involved in antiviral responses[60,62].

In the study conducted by Wakimoto and colleagues, the mRNA expression of these cytokines by PBMCs was analyzed 12 h after OV injection in rats, comparing control rats to those pretreated with CPA. In the absence of CPA (saline-treated rats), the intratumoral injection of oncolytic HSV induced significant mRNA production of IFN-α, IFN-β, IFN-γ, TNF-α, and IL-15 by PBMCs, while IL-18 mRNA levels remained unchanged. However, rats that received simultaneous or pretreatment with CPA exhibited suppressed mRNA levels of all tested cytokines within 12 h of OV injection into tumors. Notably, CPA treatment alone in the saline-treated animals appeared to induce the production of certain cytokine mRNAs, particularly IFN-γ. These findings indicated that CPA impaired the innate PBMC response to oncolytic HSV, which normally involved the production of antiviral cytokine mRNAs. It should be noted that CPA treatment, in the absence of OV, led to the induction of certain cytokines, emphasizing its complex immunomodulatory effects[54].

In-vitro and in-vivo effects of combination treatment for gliomas

Quantitative measurements were conducted to assess the in-vivo anti-cancer effects of the combination therapy involving MGH2, CPA, and irinotecan (CPT-11) in an orthotopic xenograft model of glioma using human Gli36ΔEGFR glioma cells expressing firefly luciferase. The aim was to quantitate the tumor response to different treatment regimens[54].

Athymic mice with brain glioma xenografts were treated with various combinations of intraperitoneal CPT-11, intraperitoneal CPA, and stereotactic inoculations of MGH2. Different combinations, including MGH2 with CPT-11, MGH2 with CPA, or MGH2 with both CPA and CPT-11, were tested. The activity of firefly luciferase, which correlates with cell viability, was measured in the animal brains through bioluminescence imaging over a 10-day period. Results indicated that the combination of MGH2, cyclophosphamide, and CPT-11 was the most effective in reducing luciferase activity, signifying decreased tumor cell viability, compared to all other treatment combinations. A representative image showed significantly lower bioluminescence in the brains of mice treated with MGH2 plus CPA plus CPT-11 compared to those treated with MGH2 alone. To further confirm these findings, survival time was assessed in treated mice using the same treatment schedule for virus and prodrug administration. Mice with intracerebral glioma xenografts were treated with saline, MGH2 alone, or MGH2 in combination with CPA and CPT-11. The results demonstrated a statistically significant increase in the survival time of mice treated with MGH2 plus CPA plus CPT-11 compared to the other treatment groups[63].

However, in-vitro experiments demonstrate that the addition of the activated form of CPA (4-hydroperoxy CPA) results in effects contrary to those observed *in vivo*. Therefore, we propose that these data support an initial immunosuppressive mechanism enhancing viral oncolysis, followed by CPA's anti-cancer effects, which may take several days to manifest even *in vitro*. These combined effects contribute to increased survival in animals with brain tumors and further synergize with viral oncolysis[54].

Bioconversion and activation of cyclophosphamide within gliomas

A study by Ichikawa and colleagues investigated the use of CPA in combination with oHSV (rRp450) for the treatment of gliomas, which aimed to determine the bioconversion of CPA into its active metabolites, 4-hydroxyCPA/AP, within tumor cells infected with rRp450. The results demonstrated a time-dependent increase in the concentration of 4-hydroxyCPA/AP in the supernatant of infected cells, indicating successful activation of CPA by the virus. In-vivo experiments further explored the kinetics of CPA bioconversion within tumors. Intratumoral implantation of CPA-polymer pellets followed by rRp450 inoculation resulted in prolonged and higher concentrations of activated metabolites within the tumor compared to systemic CPA administration. Peak blood levels of activated metabolites were also lower with intratumoral delivery, indicating a more targeted effect[64].

Factors affecting the outcome of combination treatment for gliomas

Despite observing a significant improvement in the oncolytic effect and a notable extension in animal survival with the CPA and OV combination treatment in studies, long-term cure was not achieved. This outcome can be attributed to several factors; an aggressive glioma cell line leading to rapid animal mortality within 2 weeks rather than 4 weeks of implantation; delayed treatment initiation on 7th day post-implantation, inefficiency in

rat glioma infection, and poor immunogenicity of D74 glioma cells. Treatment was initiated on day 7 post-implantation, at a point when tumors had already reached diameters of at least one millimeter on histological analysis; inefficient infection of rat glioma cells by the oncolytic virus; and poor immunogenicity of D74 glioma cells compared to other glioma cell lines like F98 or 9L. These factors collectively explain the inability to achieve long-term cures despite the positive outcomes seen with the CPA + OV combination treatment[65].

Conclusions

In conclusion, the management of recurrent malignant gliomas remains a significant challenge in clinical oncology. Current treatment options, while offering some benefits, fall short of providing a substantial increase in survival and often come with adverse side effects. The histopathological diversity among gliomas, the blood-brain barrier's role in limiting drug access, and the tumor's interactions with the brain further compound the difficulties in treatment. However, there is hope on the horizon with the emerging combination therapy of oncolytic herpes viruses and cyclophosphamide, which has shown increased transgene expression, enhanced viral oncolysis, and improved animal survival in experimental studies. While challenges and limitations persist, the synergy between oncolytic herpes viruses and cyclophosphamide offers a potential path forward in the treatment of recurrent malignant gliomas. Further research and clinical trials are needed to validate and refine this approach, but the prospects for improved outcomes in the battle against these aggressive brain tumors are encouraging.

Ethical approval

Ethical approval was not required for this review.

Consent

Informed consent was not required for this review.

Source of funding

Not applicable.

Author contribution

J.I.: conception and design of the study, drafting the manuscript, critical revision of the article for important intellectual content, and final approval of the version to be published. M.H.H.: acquisition of data, analysis and interpretation of data, drafting sections of the manuscript, and revising it critically for important intellectual content. A.A.: acquisition of data, drafting sections of the manuscript, revising it critically for important intellectual content, and providing final approval of the version to be published. I.M.: assistance in data collection, drafting sections of the manuscript, and revising it critically for important intellectual content. A.C.: data interpretation, drafting sections of the manuscript, and revising it critically for important intellectual content. A.I.: analysis and interpretation of data, drafting sections of the manuscript, and revising it critically for important intellectual content. T.P.: data collection and interpretation, drafting sections of the manuscript, and revising it critically for important intellectual content. A.S.: assistance in data collection, drafting sections of the manuscript, and revising it critically for important intellectual content. A.N.: analysis and interpretation of data, drafting sections of the manuscript, and revising it critically for important intellectual content. U.J.: data collection, drafting sections of the manuscript, and revising it critically for important intellectual content.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Guarantor

Javed Iqbal.

Research registration unique identifying number (UIN)

Not applicable.

Data availability statement

Not applicable.

Provenance and peer review

Not applicable.

References

[1] Hanif F, Muzaffar K, Perveen K, *et al*. Glioblastoma multiforme: a review of its epidemiology and pathogenesis through clinical presentation and treatment. Asian Pac J Cancer Prev 2017;18:3–9.
[2] Ostrom QT, Patil N, Cioffi G, *et al*. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013-2017. Neuro Oncol 2020;22(12 Suppl 2):iv1–96.
[3] Weller M, Wick W, Aldape K, *et al*. Glioma. Nat Rev Dis Primers 2015;1:15017; Published 2015 Jul 16.
[4] Stupp R, Mason WP, van den Bent MJ, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.
[5] Gilbert MR, Wang M, Aldape KD, *et al*. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol 2013;31:4085–91.
[6] Lara-Velazquez M, Al-Kharboosh R, Jeanneret S, *et al*. Advances in brain tumor surgery for glioblastoma in adults. Brain Sci 2017;7:166.
[7] Goodenberger ML, Jenkins RB. Genetics of adult glioma. Cancer Genet 2012;205:613–21.
[8] Wen PY, Kesari S. Malignant gliomas in adults. N Engl J Med 2008;359:492–507.
[9] Weller M, Le Rhun E. How did lomustine become standard of care in recurrent glioblastoma? Cancer Treat Rev 2020;87:102029.
[10] Niyazi M, Brada M, Chalmers AJ, *et al*. ESTRO-ACROP guideline "target delineation of glioblastomas. Radiother Oncol 2016;118:35–42.
[11] Harrabi SB, Bougatf N, Mohr A, *et al*. Dosimetric advantages of proton therapy over conventional radiotherapy with photons in young patients and adults with low-grade glioma. Strahlenther Onkol 2016;192:759–69.
[12] Shergalis A, Bankhead A, Luesakul U, *et al*. Current challenges and opportunities in treating glioblastoma. Pharmacol Rev 2018;70:412–45.
[13] Noch EK, Ramakrishna R, Magge R. Challenges in the treatment of glioblastoma: multisystem mechanisms of therapeutic resistance. World Neurosurg 2018;116:505–17.

[14] Totsch SK, Schlappi C, Kang KD, *et al*. Oncolytic herpes simplex virus immunotherapy for brain tumors: current pitfalls and emerging strategies to overcome therapeutic resistance. Oncogene 2019;38:6159–71.
[15] Hua L, Wakimoto H. Oncolytic herpes simplex virus therapy for malignant glioma: current approaches to successful clinical application. Expert Opin Biol Ther 2019;19:845–54.
[16] Rius-Rocabert S, García-Romero N, García A, *et al*. Oncolytic virotherapy in glioma tumors. Int J Mol Sci 2020;21:7604.
[17] Martikainen M, Essand M. Virus-based immunotherapy of glioblastoma. Cancers (Basel) 2019;11:186.
[18] Chiocca EA, Nassiri F, Wang J, *et al*. Viral and other therapies for recurrent glioblastoma: is a 24-month durable response unusual? Neuro Oncol 2019;21:14–25.
[19] Martuza RL, Malick A, Markert JM, *et al*. Experimental therapy of human glioma by means of a genetically engineered virus mutant. Science 1991;252:854–6.
[20] Glorioso JC, Cohen JB, Goins WF, *et al*. Oncolytic HSV vectors and antitumor immunity. Curr Issues Mol Biol 2021;41:381–468.
[21] Alayo QA, Ito H, Passaro C, *et al*. Glioblastoma infiltration of both tumor- and virus-antigen specific cytotoxic T cells correlates with experimental virotherapy responses. Sci Rep 2020;10:5095.
[22] Saha D, Wakimoto H, Rabkin SD. Oncolytic herpes simplex virus interactions with the host immune system. Curr Opin Virol 2016;21:26–34.
[23] Harrow S, Papanastassiou V, Harland J, *et al*. HSV1716 injection into the brain adjacent to tumour following surgical resection of high-grade glioma: safety data and long-term survival. Gene Ther 2004;11:1648–58.
[24] Rampling R, Cruickshank G, Papanastassiou V, *et al*. Toxicity evaluation of replication-competent herpes simplex virus (ICP 34.5 null mutant 1716) in patients with recurrent malignant glioma. Gene Ther 2000;7:859–66.
[25] Papanastassiou V, Rampling R, Fraser M, *et al*. The potential for efficacy of the modified (ICP 34.5(-)) herpes simplex virus HSV1716 following intratumoural injection into human malignant glioma: a proof of principle study. Gene Ther 2002;9:398–406.
[26] Andtbacka RH, Kaufman HL, Collichio F, *et al*. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 2015;33:2780–8.
[27] Markert JM, Razdan SN, Kuo HC, *et al*. A phase 1 trial of oncolytic HSV-1, G207, given in combination with radiation for recurrent GBM demonstrates safety and radiographic responses. Mol Ther 2014;22:1048–55.
[28] Ferrucci PF, Pala L, Conforti F, *et al*. Talimogene laherparepvec (T-VEC): an intralesional cancer immunotherapy for advanced melanoma. Cancers (Basel) 2021;13:1383.
[29] Nguyen HM, Saha D. The current state of oncolytic herpes simplex virus for glioblastoma treatment. Oncolytic Virother 2021;10:1–27.
[30] Zhou Z, Tian J, Zhang W, *et al*. Multiple strategies to improve the therapeutic efficacy of oncolytic herpes simplex virus in the treatment of glioblastoma. Oncol Lett 2021;22:510.
[31] Bernstock JD, Vicario N, Li R, *et al*. Safety and efficacy of oncolytic HSV-1 G207 inoculated into the cerebellum of mice. Cancer Gene Ther 2020;27:246–55.
[32] Markert JM, Medlock MD, Rabkin SD, *et al*. Conditionally replicating herpes simplex virus mutant, G207 for the treatment of malignant glioma: results of a phase I trial. Gene Ther 2000;7:867–74.
[33] Markert JM, Liechty PG, Wang W, *et al*. Phase Ib trial of mutant herpes simplex virus G207 inoculated pre-and post-tumor resection for recurrent GBM. Mol Ther 2009;17:199–207.
[34] Whisenhunt TR Jr, Rajneesh KF, Hackney JR, *et al*. Extended disease-free interval of 6 years in a recurrent glioblastoma multiforme patient treated with G207 oncolytic viral therapy. Oncolytic Virother 2015;4:33–8.
[35] Taguchi S, Fukuhara H, Todo T. Oncolytic virus therapy in Japan: progress in clinical trials and future perspectives. Jpn J Clin Oncol 2019;49:201–9.
[36] Patel DM, Foreman PM, Nabors LB, *et al*. Design of a phase I clinical trial to evaluate M032, a genetically engineered HSV-1 expressing IL-12, in patients with recurrent/progressive glioblastoma multiforme, anaplastic astrocytoma, or gliosarcoma. Hum Gene Ther Clin Dev 2016;27:69–78.
[37] Ahlmann M, Hempel G. The effect of cyclophosphamide on the immune system: implications for clinical cancer therapy. Cancer Chemother Pharmacol 2016;78:661–71.
[38] Fulci G, Breymann L, Gianni D, *et al*. Cyclophosphamide enhances glioma virotherapy by inhibiting innate immune responses. PNAS 2006;103:12873–8. .
[39] Ashkar AA, Rosenthal KL. Interleukin-15 and natural killer and NKT cells play a critical role in innate protection against genital herpes simplex virus type 2 infection. J Virol 2003;77:10168–71.
[40] Grubor-Bauk B, Simmons A, Mayrhofer G, *et al*. Impaired clearance of herpes simplex virus type 1 from mice lacking CD1d or NKT cells expressing the semi variant V alpha 14-J alpha 281 TCR. J Immunol. 2003;170:1430–4.
[41] Ahmad A, Sharif-Askari E, Fawaz L, *et al*. Innate immune response of the human host to exposure with herpes simplex virus type 1: in vitro control of the virus infection by enhanced natural killer activity via interleukin-15 induction. J Virol 2000;74:7196–203.
[42] Wakimoto H, Johnson PR, Knipe DM, *et al*. Effects of innate immunity on herpes simplex virus and its ability to kill tumor cells. Gene Ther 2003;10:983–90.
[43] Ikeda K, Wakimoto H, Ichikawa T, *et al*. Complement depletion facilitates the infection of multiple brain tumors by an intravascular, replication-conditional herpes simplex virus mutant. J Virol 2000;74:4765–75.
[44] Schiavoni G, Sistigu A, Valentini M, *et al*. Cyclophosphamide synergizes with type I interferons through systemic dendritic cell reactivation and induction of immunogenic tumor apoptosis. Cancer Res 2011;71:768–78.
[45] Mokyr MB, Place AT, Artwohl JE, *et al*. Importance of signaling via the IFN-alpha/beta receptor on host cells for the realization of the therapeutic benefits of cyclophosphamide for mice bearing a large MOPC-315 tumor. Cancer Immunol Immunother 2006;55:459–68.
[46] Wu J, Waxman DJ. Immunogenic chemotherapy: Dose and schedule dependence and combination with immunotherapy. Cancer Lett 2018;419:210–21.
[47] Doloff JC, Waxman DJ. VEGF receptor inhibitors block the ability of metronomically dosed cyclophosphamide to activate innate immunity-induced tumor regression. Cancer Res 2012;72:1103–15.
[48] Wu J, Waxman DJ. Metronomic cyclophosphamide eradicates large implanted GL261 gliomas by activating antitumor Cd8 + T-cell responses and immune memory. Oncoimmunology 2015;4:e1005521.
[49] Chen CS, Doloff JC, Waxman DJ. Intermittent metronomic drug schedule is essential for activating antitumor innate immunity and tumor xenograft regression. Neoplasia 2014;16:84–96.
[50] Wu J, Waxman DJ. Metronomic cyclophosphamide schedule-dependence of innate immune cell recruitment and tumor regression in an implanted glioma model. Cancer Lett 2014;353:272–80.
[51] Wu J, Jordan M, Waxman DJ. Metronomic cyclophosphamide activation of anti-tumor immunity: tumor model, mouse host, and drug schedule dependence of gene responses and their upstream regulators. BMC Cancer 2016;16:623.
[52] Doloff JC, Waxman DJ. Transcriptional profiling provides insights into metronomic cyclophosphamide-activated, innate immune-dependent regression of brain tumor xenografts. BMC Cancer 2015;15:375.
[53] Ikeda K, Ichikawa T, Wakimoto H, *et al*. Oncolytic virus therapy of multiple tumors in the brain requires suppression of innate and elicited antiviral responses. Nat Med 1999;5:881–7.
[54] Wakimoto H, Fulci G, Tyminski E, *et al*. Altered expression of antiviral cytokine mRNAs associated with cyclophosphamide's enhancement of viral oncolysis. Gene Ther 2004;11:214–23.
[55] Kambara H, Saeki Y, Chiocca EA. Cyclophosphamide allows for in vivo dose reduction of a potent oncolytic virus. Cancer Res 2005;65:11255–8.
[56] Hanahan D, Bergers G, Bergsland E. Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. J Clin Invest 2000;105:1045–7.
[57] Mitchell BM, Stevens JG. Neuroinvasive properties of herpes simplex virus type 1 glycoprotein variants are controlled by the immune response. J Immunol 1996;156:246–55.
[58] Hickman-Davis JM, Lindsey JR, Matalon S. Cyclophosphamide decreases nitrotyrosine formation and inhibits nitric oxide production by alveolar macrophages in mycoplasmosis. Infect Immun 2001;69:6401–10.
[59] Kodukula P, Liu T, Rooijen NV, *et al*. Macrophage control of herpes simplex virus type 1 replication in the peripheral nervous system. J Immunol 1999;162:2895–905.

[60] Karupiah G, Xie QW, Buller RM, *et al*. Inhibition of viral replication by interferon-gamma-induced nitric oxide synthase. Science 1993;261: 1445–8.
[61] Leib DA, Harrison TE, Laslo KM, *et al*. Interferons regulate the phenotype of wild-type and mutant herpes simplex viruses in vivo. J Exp Med 1999;189:663–72.
[62] Fujioka N, Akazawa R, Ohashi K, *et al*. Interleukin-18 protects mice against acute herpes simplex virus type 1 infection. J Virol 1999;73:2401–9.
[63] Tyminski E, Leroy S, Terada K, *et al*. Brain tumor oncolysis with replication-conditional herpes simplex virus type 1 expressing the prodrug-activating genes, CYP2B1 and secreted human intestinal carboxylesterase, in combination with cyclophosphamide and irinotecan. Cancer Res 2005;65:6850–7.
[64] Ichikawa T, Petros WP, Ludeman SM, *et al*. Intraneoplastic polymer-based delivery of cyclophosphamide for intratumoral bioconversion by a replicating oncolytic viral vector. Cancer Res 2001;61:864–8.
[65] Tzeng JJ, Barth RF, Orosz CG, *et al*. Phenotype and functional activity of tumor-infiltrating lymphocytes isolated from immunogenic and nonimmunogenic rat brain tumors. Cancer Res 1991;51: 2373–8.