From Bench to Bedside, the Current State of Oncolytic Virotherapy in Pediatric Glioma

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Glioma continues to be a challenging disease process, making up the most common tumor type within the pediatric population. While low-grade gliomas are typically amenable to surgical resection, higher grade gliomas often require additional radiotherapy in conjunction with adjuvant chemotherapy. Molecular profiling of these lesions has led to the development of various pharmacologic and immunologic agents, although these modalities are not without great systemic toxicity. In addition, the molecular biology of adult glioma and pediatric glioma has been shown to differ substantially, making the application of current chemotherapies dubious in children and adolescents. For this reason, therapies with high tumor specificity based on pediatric tumor cell biology that spare healthy tissue are needed. Oncolytic virotherapy serves to fill this niche, as evidenced by renewed interest in this domain of cancer therapy. Initially discovered by chance in the early 20th century, virotherapy has emerged as a viable treatment option. With promising results based on preclinical studies, the authors review several oncolytic viruses, with a focus on molecular mechanism and efficacy of these viruses in tumor cell lines and murine models. In addition, current phase I clinical trials evaluating oncolytic virotherapy in the treatment of pediatric glioma are summarized.

KEY WORDS: Pediatric glioma, Oncolytic virotherapy, Preclinical research, Neuro-oncology

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Gliomas, divided into low-grade glioma (LGG) and high-grade glioma (HGG), are the most common tumors of the central nervous system (CNS) in children and adolescents.[1] Surgical excision is typically the first-line treatment for those gliomas amenable to resection. For HGGs, current treatment strategies are limited in scope, with radiotherapy and supportive care serving to only improve quality of life but rarely survival, as most patients die within 1 yr of diagnosis.[1] The molecular diversity of these tumors makes developing effective chemotherapeutic agents challenging, with existing agents being associated with many comorbidities.

Oncolytic virotherapy is a newly emerging therapeutic tool in cancer treatment. Combining tumor cell lysis with local immune stimulation, oncolytic viruses have been demonstrated to be effective in a variety of cancers.[2] Virus pathogenicity, susceptibility to transgenic editing, proinflammatory response, and tumor cell selectivity are among the many aspects that make virotherapy a favorable treatment option.[3] Virotherapy research has gained traction in the realm of adult glioma, with phase I

ABBREVIATIONS: APOBEC3A, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3A; **CNS,** central nervous system; **CPA,** cyclophosphamide; **CSC,** cancer stem-like cell; **CTHRC1,** collagen triple helix repeat containing 1; **DIPG,** diffuse intrinsic pontine glioma; **DUSP3,** dual specificity protein phosphatase 3; **E1A,** early region 1A; **GFP,** green fluorescence protein; **GM-CSF,** granulocyte-macrophage colony-stimulating factor; **H-1PV,** H-1 parvovirus; **HGG,** high-grade glioma; **HSV,** herpes simplex virus; **IL23A,** interleukin 23 subunit alpha; **IL4I1,** interleukin 4 induced 1; **LAMA1,** laminin subunit alpha 1; **LGG,** low-grade glioma; **MB,** medulloblastoma; **MMP1,** matrix metallopeptidase 1; **MOI,** multiplicity of infection; **MRI,** magnetic resonance imaging; **MV,** measles virotherapy; **oHSV,** oncolytic HSV; **PPM1F,** protein phosphatase Mg^{2+}/Mn^{2+}-dependent 1F; **PVSRIPO,** recombinant nonpathogenic poliorhinovirus chimera; **RUNX1,** runt-related transcription factor 1; **SVV,** Seneca Valley virus; **TLR3,** Toll-like receptor 3; **TRIM5,** tripartite motif containing 5

clinical trials showing promising results.[4,5] Given that pediatric neoplasms biologically differ from adult tumors with respect to cellular origin and molecular genetics,[6] the development of oncolytic viruses in pediatric glioma is only recently coming to light. In the last decade, a number of preclinical studies have demonstrated the antitumor effect of oncolytic viruses in pediatric glioma; this includes direct lysis, inhibition of tumor cell migration and invasion, and localized inflammatory upregulation.[7-15]

In this review, the authors provide a discussion of pediatric oncolytic virotherapy for HGG with respect to the findings of recent preclinical studies, along with an overview of early pilot studies.

ONCOLYTIC VIROTHERAPY

The oncolytic properties of viruses were discovered well before the characterization of viruses themselves. In 1904, George Dock published a series of 65 patients in which the presence of concomitant infection appeared to have a transient improvement in symptoms caused by underlying malignancy. Dock recounted a specific patient who experienced a temporary remission from acute leukemia after infection with influenza,[16] and similar oncolytic properties were found in other leukemia patients after measles infection in the latter half of the 20th century.[17,18] As developments in chemotherapy became more promising, interest and research in oncolytic virotherapy was met with decline well into the 1970s to 1780s.[19]

With the advent of recombinant DNA technology in the 1990s, genetic engineering prompted renewed interest in oncolytic virotherapy, enabling improved tumor specificity with less collateral damage to normal host tissue.[19] Specificity was accomplished by designing viruses to target tumor-specific mutations, signaling pathways, and cell surface antigens. This was made possible by the use of reporter genes that enable the visualization and quantification of viral spread.[19,20] To date, there exists an increasing variety of genetically engineered oncolytic viruses and strategies for tumor-specific targeting and replication, many of which perform best in combination with other therapeutic techniques.[21]

PRECLINICAL STUDIES

A number of preclinical studies have begun to emerge with respect to evaluating the efficacy and molecular biology of oncolytic virotherapy in pediatric glioma. Utilizing pediatric glioma cell lines and murine models, these studies provide valuable information regarding the translational potential of this treatment modality. Relevant studies were identified based on a literature search utilizing the terms "oncolytic virotherapy pediatric glioma" in PubMed and MEDLINE databases as well as from other sources including reference lists of published articles. Articles not evaluating glial tumors were excluded with the exception of medulloblastoma, a common pediatric malignancy formally classified as a glioma.[22] The selected studies were published between 2010 and 2019, and they are organized based on the specific virus type studied. Table 1 provides a summary of the preclinical studies.

Herpes Simplex Virus

In a study by Cockle et al,[7] the oncolytic mechanism of herpes simplex virus (HSV) 1716 was evaluated in both pediatric HGG and diffuse intrinsic pontine glioma (DIPG) cell lines. While primarily thought to inhibit tumor growth and spread by lysis, the authors identified HSV 1716 to also affect cellular invasion and migration independent of its cytotoxicity. The mechanism of inhibition is multifold, with HSV 1716 being shown to alter cellular morphology, velocity, and polarity; specifically, the pediatric HGG cells after treatment appeared unable to generate coordinated contractile forces required for motility. HSV 1716 increased levels of acetylated tubulin in pediatric HGG and DIPG cell lines, serving to stabilize and therefore prevent the active polymerization and depolymerization necessary for microtubule-mediated tumor migration. In addition, utilizing an orthotopic xenograft of DIPG, intracranial injections with HSV 1716 demonstrated reduced infiltration of tumor cells into surrounding structures within the brainstem. Despite these findings, a recent trial (NCT02031965) in which patients receive intratumoral/peritumoral injection of HSV 1716 after surgical resection of recurrent HGG was terminated.

Studebaker et al[8] also investigated the oncolytic efficacy of an attenuated herpes simplex 1 vector rRp450 in medulloblastoma (MB) cell lines derived from molecular subtype groups 3 and 4. These subtypes are associated with the highest propensity to metastasize, thus having the poorest prognosis. Herpes simplex vector rRp450 was selected, as opposed to other oncolytic HSV (oHSV) mutant variants, as this vector contains intact copies of the neuroviurulence gene that expresses CYP2B1. This is an enzyme that activates cyclophosphamide (CPA), a chemotherapeutic prodrug. Once infected by rRp450, cells can activate CPA. This results in the delivery of cytotoxic metabolites within the tumor microenvironment. Survival times were observed to be significantly prolonged in virus-treated mice, in some cases reaching the experimental endpoint (100 d). Based on the Kaplan-Meier curve analysis, the median survival of mice bearing D283 tumor cell line (group 3) was 82 d compared with 60 d in vehicle-treated mice ($P = .0059$). The median survival for oHSV-treated D425 tumor-bearing mice (group 4) was 54 vs 20 d for vehicle-treated mice ($P < .0001$). No adverse symptoms attributable to the virus were observed in any of the rRp450-treated mice. Moreover, H&E staining and pathologist review of those mice surviving to 100 d were tumor-free. With respect CPA sensitivity, MB cells infected with rRp450 in the presence of CPA experienced significantly greater cell death. Therefore, the findings of this study suggest oHSV rRp450 to be efficacious against human MB cell lines in orthotopic xenograft models.

TABLE 1. Summary of Preclinical Studies

Study	Virus	Cell line	Proposed mechanism
Cockle et al, 2017[7]	HSV1716	HGG, DIPG	• Inhibition of cellular migration, invasion • Direct lysis
Studebaker et al, 2017[8]	HSV rRp450	MB (groups 3 and 4)	• Bioactivator of CPA • Direct lysis
Friedman et al, 2018[23]	HSV G207, M002	HGG (D456)	• Increased nectin-1 expression enhances tumor infectivity
Friedman et al, 2016[9]	HSV G207, M002	MB (D425, D341)	• Inhibition of $CD133^+$ and $CD15^+$ cancer stem-like cells
Josupeit et al, 2016[10]	H-1PV	HGG ($CD133^+$, $CD133^-$)	• Gene modulation • Inflammatory upregulation • Direct lysis
Lacroix et al, 2014[11]	H-1PV	MB (MED8A, D425, D458, UW228-2, DAOY, ONS76).	• Gene modulation • Inhibition of cell differentiation and migration • Direct lysis
Hutzen et al, 2014[12]	MV-E:A	MB (D283med, D425med)	• Vector for anti-angiogenic agents (no enhanced viral cytotoxicity)
Studebaker et al, 2010[13]	MV-GFP	MB (D283med, D341med, UW288-1, UW426, DAOY)	• CD46-mediated viral entry • Syncytia formation and cell lysis
Liu et al, 2013[14]	SVV-002, SVV-GFP	GBM (1128, 1406, 1502, 1621, 2305), AA (1227)	• Infectivity mediated by sialic acid residues • Direct lysis
Martínez-Vélez et al, 2019[15]	Delta-24-RGD	DIPG (TP80, TP54), HGG (CHLA-030AA, PBT-24)	• Enhanced lymphocytic infiltration of tumor cells • Direct lysis

Friedman et al[9] investigated whether oHSV therapy could effectively infect and kill multiple aggressive pediatric MB cell lines, including cancer stem-like cells (CSCs) marked by antigens $CD133^+$ and $CD15^+$. Regions of hypoxia within brain tumors serve to drive the CSC phenotype, leading to heightened invasiveness, angiogenesis, and ultimately metastasis. Thus, it was hypothesized that targeting CSCs along with MB cells could improve outcomes and reduce morbidity in some aggressive pediatric medulloblastomas. The data demonstrated that MB neurospheres are highly sensitive to killing by G207 and M002 HSV strains both in Vitro and in Vivo, including the highly metastatic group 3 tumor cell lines D425 and D341. In mice with D425 tumors, the median survival time was significantly prolonged following administration of G207 (20.5 ± 1.5 vs 13.8 ± 0.2 d; $P = .001$) or M002 (27.9 ± 7.2 vs 15.7 ± 1.0 d; $P = .008$) HSV strains. The median survival time was also prolonged in mice with D341 tumors after treatment with G207 (36.0 ± 3.3 vs 21.0 ± 1.4; $P < .001$) or M002 (35.2 ± 3.4 vs 21.0 ± 1.4; $P < .001$). Furthermore, the study did not demonstrate resistance in either $CD133^+$ or $CD15^+$ cells, suggesting CSCs are amenable to oHSV, which as aforementioned have been shown to propagate tumors, resist traditional therapies, and portend a worse prognosis.

In another study by Friedman et al,[23] it was found that G207 and M002 HSV strains were more effective in patient-derived pediatric malignant brain tumor than adult glioblastoma xenografts. This was determined to be correlated with nectin-1 (CD111) expression, with flow cytometry demonstrating increased expression in pediatric high-grade tumors (53.4%-98.8%) than in adult tumors (3.5%-76.2%). A cell surface adhesion molecule, nectin-1, facilitates HSV cell entry. Given that a significantly greater number of pediatric tumor cells express more nectin-1 than adult tumor cells ($P = .0005$), this indicates that pediatric tumor cells have greater susceptibility to HSV infection. This is in agreement with other findings of the study, which demonstrated significantly greater adult tumor cell survival after 72 h when compared to pediatric tumor cells for both G207 ($P = .0002$) and M002 ($P < .0001$) infections. After a single dose of M002, median survival time increased in mice bearing pediatric glioblastoma D456 (19.0 ± 0.4 to 30.0 ± 3.8 d, $P = .004$), with G207 only trending toward significance (21.0 ± 2.1 d, $P = .08$). However, the greatest survival conferred was in pediatric embryonal tumor X21415, which exhibits greater nectin-1 expression than D456. The findings of these studies suggest that oHSV therapy is multifaceted, such that it structurally inhibits tumor cell migration and has direct oncolytic

properties. Nectin-1 expression may also be a useful predictive biomarker of tumor responsiveness to oHSV. In addition, oHSV may serve as a prodrug bioactivator and was shown to prolong survival time in mice without adverse effects. Currently, HSV G207 is being evaluated alone or with radiation in children with progressive or recurrent supratentorial tumors (NCT02457845).

Parvovirus

Josupeit et al[10] evaluated the antineoplastic efficacy of oncolytic protoparvovirus H-1PV on both pediatric and adult HGG stem cell neurospheres. The cytotoxic effects of H-1PV have already been demonstrated in rat models, but data are lacking in both adult and pediatric HGG stem cell cultures. The study found that oncolytic parvovirus H-1 was cytotoxic to both $CD133^+$ and $CD133^-$ HGG cell lines. The mechanism of H-1PV resistance was also explored, with H-1PV infectivity or resistance being found to correlate with dysregulation of distinct cellular genes. Transcriptional analysis revealed a set of 201 genes that were differentially expressed in permissive versus resistant cultures. Among them are genes for positive and negative regulators of the parvoviral life cycle, regulators of the innate immune response, and restriction factors for H-1PV infection. Several of these gene products are known to act as master regulators or key effectors of innate antiviral immune response such as TGF-β, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3A (APOBEC3A), tripartite motif containing 5 and 38 (TRIM5 and TRIM38), collagen triple helix repeat containing 1 (CTHRC1), and Toll-like receptor 3 (TLR3). Of special importance is APOBEC3A, which, as part of the innate immune response, is thought to restrict single-stranded DNA viral replication, including some of the Parvoviridae family, thus providing insight into tumor susceptibility with respect to genetic differences in glioma cell lines. In addition to these findings, the tumor-suppressing effect of H-1PV was found to be dose-dependent, as the fraction of animals failing to show any tumor development increased with the size of the viral inoculum.

Lacroix et al[11] evaluated the applicability of oncolytic H-1 parvovirus (H-1PV) in the treatment of MB cell lines in Vitro with the goal of identifying target genes associated with virus-induced cytotoxicity. Out of 6 MB lines tested, 5 demonstrated efficient H-1PV multiplication, time-dependent suppression of growth, and eventual cell death. Among the genes consistently upregulated during H-1PV infection, some may play relevant roles in virus-host cell interactions. These genes include interleukin 4 induced 1 (IL4I1) and interleukin 23 subunit alpha (IL23A), which are involved in the innate antiviral immune response, as well as matrix metallopeptidase 1 (MMP1) and protein phosphatase Mg^{2+}/Mn^{2+}-dependent 1F (PPM1F), which contribute to cellular migration. Lastly, genes inducing neuronal differentiation, such as runt-related transcription factor 1 (RUNX1) or dual specificity protein phosphatase 3 (DUSP3), were identified. The only gene found to be significantly repressed as early as 24 h after H-1PV infection in all responsive MB cell lines encodes laminin subunit alpha 1 (LAMA1), a potent mitogen in granule cell precursors. Furthermore, 20 cellular genes were identified to have repressed transcription within the first 72 h after H-1PV infection. These genes are involved in controlling the neural progenitor state in early embryonic development. H-1PV-induced repression of genes involved in Wnt signaling prior to cell death was also demonstrated.

Parvovirus appears to impart its oncolytic properties by genetic modulation, causing upregulation of local inflammatory mediators and suppression of mitotic factors rather than direct tumor cell lysis. Parvovirus may be limited against specific cell lines, given the potential lack of genetic susceptibility or future resistance development.

Measles Virus

Hutzen et al[12] investigated whether the addition of angiogenesis inhibitors could further enhance the efficacy of oncolytic measles virotherapy (MV) in MB given the high vascularity of these lesions. Endostatin (E) and angiostatin (A) were selected as broad-spectrum inhibitors of angiogenesis. The authors developed oncolytic MVs that encode either human (h) or mouse (m) variants of E: A fusion proteins, as they display enhanced antiangiogenic activity and prolonged half-lives compared to either inhibitor expressed individually. These engineered viruses were termed MV-hE: A and MV-mE: A. In Vivo, a single low-dose injection of either MV-hE: A or MV-mE: A delivered intratumorally resulted in the downregulation of multiple angiogenic modulators and decreased local blood vessel formation; despite these initially promising observations, both MV-hE: A and MV-mE: A viruses failed to show any difference in significantly prolonging survival in the mouse xenograft models of MB compared to MV without angiogenesis inhibitors. It is believed that the initial antiangiogenic effects dissipated over time, suggesting pockets of tumor cells that escaped MV oncolysis without vascular inhibition impeding cell growth. This notion is supported by the observation of small foci of active intratumor MV replication. This suggests that either increasing viral administration or modifying the dosing schedule to broaden the scope of virus spread may provide added benefit.

Studebaker et al[13] investigated the efficacy of MV in treating intracerebral MB in 5 different human cell lines. The Edmonston vaccine strain of MV was selected given that it preferentially uses CD46 as a receptor, which is highly expressed in multiple tumor types. A modified version of this virus containing the green fluorescence protein (GFP) gene was utilized as a marker of infection creating MV-GFP, with the presence of green fluorescence indicating adequate viral involvement within tumor tissue. The killing of cells was time and dose dependent, with full cytotoxicity evident within 72 h. Cell death was seen at multiplicity of infection (MOI) as low as 0.1, and essentially complete killing (>80%) was seen at MOI of 1.0. All cell lines had >90% cell death at 120 h when an initial MOI of 10 was used. In mice containing the D283 cell line, MV-GFP intratumor injection

significantly prolonged survival when compared to inactivated virus-treated controls ($P < .001$). Postinfection autopsy and histological examination did not reveal any metastatic disease, with complete tumor ablation being evident in 8 of 12 MV-GFP-treated mice. In contrast, continued growth and mass effect was noted in sham mice, given mitotically active tumor cells with leptomeningeal spread and adjacent brain invasion. Bioluminescence signaling demonstrated significantly decreased tumor activity in MV-GFP treated at several time points posttreatment (8 d, $P < .05$; 15 d, $P < .05$; 29 d, $P < .005$).

MV therapy, therefore, could be applied to the tumor bed following surgical resection to target microscopic residual disease. This approach may either serve as an adjuvant or potentially reduce the need for radiation and chemotherapy; although multiple barriers to MV therapy exist including thoroughly vetting against adverse effects.

Picornavirus

Studying an oncolytic picornavirus, Liu et al[14] evaluated the therapeutic efficacy of Seneca Valley virus (SVV)-001 in pediatric gliomas. This virus was chosen since it can be administered through intravenous injection and bypass the blood-brain barrier. SVV-001 was found to replicate in and effectively kill primary cultures, preformed neurospheres, and self-renewing stem-like single glioma cells without harming healthy brain parenchyma, extending survival significantly. It was observed that the contents of sialic acids correlate with SVV-001 susceptibility in glioblastoma xenograft tumors. Mechanistically, the authors identified α2,3- and α2,6-sialic acids as essential components of SVV-001 infectivity. This was confirmed by dose-dependent, neuraminidase-induced suppression of SVV-GFP infection, which cleave terminal and internal sialic acid residues. Identifying the α2,3- and α2,6-linked sialic acids is an important leap forward with respect to discovering SVV-001 receptors that may be utilized as potential markers of viral susceptibility in pediatric glioblastomas.

Adenovirus

Martínez-Vélez et al[15] studied the antitumor potential for Delta-24-RGD in pediatric HGG and DIPGs. Delta-24-RGD is a tumor-selective, replication-competent oncolytic adenovirus that has already demonstrated antineoplastic effects in adult gliomas. This study showed that Delta-24-RGD has the ability to replicate in tumor cell lines and impart a significant antitumor effect. This is evidenced by the robust expression of early region 1A (E1A), an early protein and regulator of the viral life cycle, and fiber, which is a late protein. Compared to DIPG, viral replication was superior in pediatric HGG cell lines ($P = .03$). Survival was also shown to be extended after intratumor virus injection in 2 orthotopic models of DIPG (TP80 and TP54) and 2 models of pediatric HGG (CHLA-030AA and PBT-24). Survival curve analysis showed an increased survival of an average of 40 d ($P = .024$, log-rank test) in mice bearing the T80 cell line. The TP54 cell line exhibited an increased median survival of 95.5 from 83.5 d ($P = .04$, log-rank test). An increased overall survival of 53 d was observed in Delta-24-RGD-treated mice bearing CHLA-03-AA ($P < .0001$, log-rank test), with a median survival of 100.5 d seen in treated PBT-24 mice ($P = .0013$, log-rank test). In addition to its oncolytic effect, Delta-24-RGD administration triggered an antitumor immune response in 2 different DIPG murine models by increasing lymphocyte infiltration in the brain, suggesting its usage would pair well with existing immunotherapy treatments. The findings of this study have prompted the start of a phase I/II clinical trial,[24] with preliminary data indicating its administration is safe in the pediatric population.[25]

ONGOING TRIALS

Several trials have been initiated that are looking to evaluate the efficacy of oncolytic virotherapy within the pediatric population. Described briefly below, most are actively recruiting patients and seek to determine the safety of inoculating specific oncolytic viruses, and in some cases with adjuvant chemotherapy, into children with gliomas (Table 2). Trials are initiated based on the findings of preclinical studies or clinical trials involving adult patients or other cancer types.

Tejada et al[24] have initiated a phase I, unicentric, nonrandomized clinical trial (NCT03178032) to evaluate the safety and efficacy of intratumoral stereotactic injection of the oncolytic adenovirus DNX-2401 in children with newly diagnosed DIPG. After 3 to 4 wk, patients will receive standard of care including radiotherapy and/or chemotherapy. Primary outcome measures include determining the safety, tolerability, and toxicity of DNX-2401, looking specifically for hematologic and neurological toxicity. Secondary outcome measures include survival, tumor response on magnetic resonance imaging (MRI), and quality of life 1 yr after virus injection. The initiation of this trial was based on the promising findings of the preclinical study published by Martínez-Vélez et al.[15]

Another phase I clinical trial (NCT02444546) seeks to study the side effects and maximum tolerated dose of wild-type reovirus given in conjunction with sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF), in younger patients with refractory or recurrent HGG. An important hematopoietic growth factor and immune modulator, it is theorized that GM-CSF may augment the oncolytic activity of wild-type reovirus, which has been demonstrated in a murine model of pancreatic cancer.[26] Patients will receive sargramostim on days 1 and 2 of treatment subcutaneously, and they will receive wild-type reovirus over 60 min on days 3 and 5 intravenously. This treatment course will repeat every 28 d for a total of 12 courses given an absence of obvious toxicity or disease progression.

A phase I trial (NCT03330197) sponsored by Ziopharm Oncology seeks to study Ad-RTS-hIL-12, an adenoviral vector engineered to express human IL-12 in the presence of oral

TABLE 2. Ongoing and Past Clinical trials

NCT number	Title	Phase	Primary or recurrent	Diagnostic method
NCT03178032	Phase I trial of DNX-2401 for diffuse intrinsic pontine glioma newly diagnosed in pediatric patients	I	Primary	MRI
NCT02444546	Phase 1 study of replication competent reovirus (Reolysin®) in combination with GM-CSF in pediatric patients with relapsed or refractory brain tumors	I	Primary and recurrent	Biopsy (unless DIPG on MRI)
NCT03330197	A phase I study of Ad-RTS-hIL-12, an inducible adenoviral vector engineered to express hIL-12 in the presence of the activator ligand veledimex in pediatric brain tumor subjects	I	Primary and Recurrent	Biopsy (unless DIPG on MRI)
NCT03043391	Phase Ib study of oncolytic polio/rhinovirus recombinant against recurrent malignant glioma in children	Ib	Recurrent	Biopsy and MRI
NCT02457845	Phase I clinical trial of HSV G207 alone or with a single radiation dose in children with recurrent supratentorial brain tumors	I	Primary or recurrent	Biopsy
NCT02031965	A phase I study of intratumoral/peritumoral herpes simplex virus-1 mutant HSV1716 in patients with refractory or recurrent high grade gliomas (HGG)	Terminated	Primary or recurrent	Biopsy

DIPG = diffuse intrinsic pontine glioma; MRI = magnetic resonance imaging; GM-CSF = granulocyte-macrophage colony-stimulating factor; HGG = high-grade glioma.

veledimex, in pediatric patients with supratentorial glioma or DIPG. Veledimex functions as an activator ligand that induces IL-12 production, serving to produce this interleukin only in tumor cells infected by the oncolytic adenovirus, thereby avoiding the toxicity associated with systemic IL-12 treatment.[27] Patients who are scheduled for tumor resection will receive a single dose of veledimex prior to surgery, and Ad-RTS-hIL-12 is administered by free-hand injection. Oral veledimex will be continued for 14. Patients with DIPG will receive Ad-RTS-hIL-12 via stereotactic injection and also continue oral veledimex for 14 d. Primary endpoints include identifying the safety and tolerability of intratumoral Ad-RTS-hIL-12 and oral veledimex, with secondary endpoints assessing overall survival, tumor response, IL-12 and veledimex quantification within the blood and brain tumor. Evidence of the safety and efficacy of this treatment for glioma was demonstrated previously in a clinical trial (NCT02026271) in adult patients with recurrent HGG.[27]

Recombinant nonpathogenic poliorhinovirus chimera (PVSRIPO) was found to increase survival in adults with HGG in a recent clinical trial (NCT01491893).[28] For this reason, a phase Ib clinical trial (NCT03043391) evaluating the efficacy of PVSRIPO has been initiated for pediatric patients with HGG. PVSRIPO is a live-attenuated poliovirus type 1 (Sabin) vaccine with its cognate internal ribosome entry site replaced with that of human rhinovirus type 2, causing an inability of this virus to infect and translate within neurons; instead, PVSRIPO relies on CD155 as its ligand, which is highly upregulated on malignant cells.[28] Utilizing convection-enhanced delivery, which generates a pressure gradient within an infusion catheter to deliver therapeutics directly into selected brain or tumor tissue,[29] this study aims to deliver PVSRIPO within the enhancing portion of the tumor. The percentage of participants with unacceptable toxicity is the primary outcome measure, with 2-yr overall survival being the secondary outcome measure.

While a phase I trial (NCT02031965) for HSV 1716 was terminated, a phase I trial for another herpes virus strain, HSV G207, is ongoing (NCT02457845). Preliminary findings for 6 subjects (5 glioblastoma, 1 anaplastic astrocytoma) indicate no serious adverse events, with evidence of sustained radiographic response to the virus seen more than 12 mo after virus injection in 5 patients. This clinical trial is utilizing stereotactic placement of intratumoral catheters for continuous infusion delivery of the oncolytic virus, which has been shown to be feasible and safe with minimal complications.[30]

CONCLUSION

Pediatric HGG remains a devastating disease, with poor outcomes despite efforts from provider care teams. Current chemotherapeutic strategies are not without fault, extending survival marginally at the expense of systemic toxicity. Oncolytic virotherapy serves as a promising treatment modality that may circumvent these pitfalls, given its ability to target tumor cells specifically while sparing surrounding brain parenchyma as evidenced by the preclinical studies described. The findings of these preclinical studies also provide further evidence of the effectiveness of viral tumor cell infectivity, suggesting both a lytic and triggered local immunomodulatory response are responsible for its ability to prolong survival in murine models and reduce tumor burden. In addition, viruses may be utilized as vectors for targeted immunologic and drug therapies. This provides practitioners reassurance when designing clinical trials, with several phase I trials already in progress. Still in its infancy, oncolytic virotherapy provides a new and promising approach to an otherwise stubborn pathology.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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