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Stereotactic Placement of Intratumoral Catheters for Continuous Infusion Delivery of Herpes Simplex Virus -1 G207 in Pediatric Malignant Supratentorial Brain Tumors

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Abstract

OBJECTIVE: The engineered herpes simplex virus-1 G207, is a promising therapeutic option for central nervous system tumors. The first-ever pediatric phase 1 trial of continuous-infusion delivery of G207 via intratumoral catheters for recurrent or progressive malignant brain tumors is ongoing. In this article, we describe surgical techniques for the accurate placement of catheters in multiple supratentorial locations and perioperative complications associated with such procedures.

METHODS: A prospective study of G207 in children with recurrent malignant supratentorial tumors is ongoing. Preoperative stereotactic protocol magnetic resonance imaging was performed, and catheter trajectories planned using StealthStation planning software. Children underwent placement of 3–4 silastic catheters using a small incision burr hole and the Vertek system. Patients had a preinfusion computed tomography scan to confirm correct placement of catheters.

RESULTS: Six children underwent implantation of 3–4 catheters. Locations of catheter placement included frontal, temporal, parietal, and occipital lobes, and the insula and thalamus. There were no clinically significant perioperative complications. Postoperative computed

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tomography scans coupled with preoperative MRI scans demonstrated accurate placement of 21 of 22 catheters, with 1 misplaced catheter pulled back to an optimal location at the bedside. One patient had hemorrhage along the catheter tract that was clinically asymptomatic. Another patient had cerebrospinal fluid leak from a biopsy incision 9 days after surgery that was oversewn without complication.

CONCLUSIONS: The placement of multiple intratumoral catheters in pediatric patients with supratentorial tumors via frameless stereotactic techniques is feasible and safe. Intratumoral catheters provide a potentially effective route for the delivery of G207 and may be employed in other trials utilizing oncolytic virotherapy for brain tumors.

Keywords

Oncolytic virotherapy; Pediatric brain tumors; Recurrent brain tumors; Stereotactic surgery

INTRODUCTION

Central nervous system tumors, accounting for almost one fourth of all pediatric malignancies, are the most common solid neoplasm in children and constitute a leading cause of both morbidity and mortality in children.^{1,2} Outcomes for children with low grade, localized tumors tend to be excellent, but a significant subset of patients with high-grade malignancies have very poor outcomes even after conventional therapies (e.g., surgical resection, chemotherapy, or radiation), which provide only a brief period of disease control for patients with high grade recurrent tumors.^{3,4} Furthermore, survivors who received traditional therapy often suffer damaging disability as a result, including hormone dysfunction, neurosensory impairment, and neurocognitive deficits.^{5–7} Thus, there is an urgent need for novel treatments that improve patient outcomes and reduce adverse effects in children.

Pediatric brain tumors are suitable targets for interventions utilizing conditionally replicating viruses; that is, viruses that kill actively-dividing tumor cells while sparing the postmitotic, nondividing normal brain cell population.^{8–10} Among these, attenuated herpes simplex virus (HSV) bears numerous advantages as an antineoplastic therapy for brain tumors. It is now possible to engineer an HSV-1 capable of selective replication in brain tumor cells, as both essential and nonessential genes for neurotropic replication in the brain and brain tumors have been identified.^{11–14} The attenuated virus remains immunogenic, promoting danger signals that can reverse tumor immune circumvention, augment cross-presentation of tumor antigens, and fuel an antitumor immune response, even in the absence of virus permissivity.^{15,16} Finally, in the unlikely event that a mutant virus produces harmful effects in normal brain tissue, these viral constructs can be controlled by readily available antiviral agents (e.g., acyclovir) since they retain the thymidine kinase gene.

Notably, 3 phase 1 clinical trials have demonstrated the safety of the engineered HSV-1 G207 virus in adult patients.^{17–19} In addition, preclinical studies have shown that a variety of pediatric tumor types—including neural and glial tumors—express the primary HSV entry receptor, nectin-1 (CD111) an adhesion molecule, and that these tumors are highly sensitive to engineered HSVs (i.e., G207) both in vitro and in vivo, suggesting that the efficacy of

such treatments may be highest in the pediatric population.^{10,20–22} However, a critical and unappreciated obstacle to this approach is the ability to efficiently deliver virotherapeutics, such as HSV G207, to the brain such that the treatment effect is maximized while adverse effects are minimized. Accordingly, herein we highlight the stereotactic techniques developed and employed in our pediatric cohort, primarily regarding catheter placement directly into recurrent or progressive supratentorial malignant tumors for the therapeutic intratumoral inoculation of G207.

METHODS

Our institutional review board examined and approved the studies described in this article in accordance with our assurance of compliance approved by the U.S. Department of Health and Human Services. Informed consent, and, when applicable, assent, was obtained from all patients and guardians prior to being screened for treatment.

Catheter Implantation Planning and Procedure

Preoperative magnetic resonance imaging (MRI) scans were evaluated for each patient. Based on this imaging and with the aid of StealthStation planning software (Medtronic Inc., Minneapolis, Minnesota, USA), catheter targets were designated within areas of contrast enhancing tumor and at least 1 cm from the ventricles, cisterns, or previous resection cavity. Catheters were passed in a trajectory to ensure the longest possible passage through tumor to allow any reflux back along the catheter tract to remain within the tumor. Every attempt was made to distribute catheters throughout the tumors to allow maximum coverage with the virus. Entry points were selected to ensure ease of access to the targets while avoiding eloquent tissue, large blood vessels, ventricles, resection cavities, and cisterns (Figure 1).

Patients were brought to the operating room where they were anesthetized using standard procedures. They were positioned with rigid pin fixation and were registered with StealthStation planning software. The Stealth Vertek system (Medtronic Inc.) was used to identify entry points where a stab incision was used to open the skin, and a drill was used to make small burrholes large enough to ensure free passage of the biopsy needle or catheter. The surface of the dura was coagulated with a monopolar stylet and then perforated with the stylet without cauterization. Following frozen section demonstration of recurrent tumor, up to 4 silastic catheters (PIC-030 Neuro-Infusion Catheter; Sophysa USA, Crown Point, Indiana, USA, [30 cm x 2.0 mm outer diameter, 1.00 mm inner diameter], equipped with a stainless-steel stylet and a 6 French compression hub) were prepared for placement in stereotactically predefined coordinates of tumor (enhancing or non-enhancing regions). Patients did not undergo tumor resection. The silastic catheters were marked to a previously measured distance, flushed with Dulbecco's phosphate-buffered saline (DPBS) in 10% glycerol (Alanza Inc., Round Rock, Texas, USA) to ensure easy removal of the stylet, and placed through the Stealth Vertek guide to the target locations. The catheter was immobilized at the bone edge, the stylet was carefully removed, and the catheter was then tunneled subcutaneously (Figure 2). A purse string nylon stitch was placed at the exit site, the catheter was flushed with DPBS in 10% glycerol, and the wounds were closed. The patients were then extubated and observed overnight in the pediatric intensive care unit. The

following morning, a postoperative head computed tomography (CT) scan was obtained to confirm the location of each catheter within the tumor. If necessary, the surgeon adjusted the position of the catheter tip by slightly withdrawing it to a more desirable location.

HSV-1 G207 Preparation and Infusion

G207 is a genetically engineered HSV-1 that has been demonstrated to be aneurovirulent secondary to deletions of both copies of the γ 134.5 gene and a disabling lacZ insertion at U_L39, which encodes for the large subunit of the viral ribonucleotide reductase.¹⁴ G207 is supplied by Aettis Inc. (Bala Cynwyd, PA), in sterile, labeled 1.0 mL cryovials containing 0.12 mL of G207 suspended in the storage buffer, DPBS and 10% glycerol. The vials remain frozen at -60°C or below until use. Once thawed, the virus maintains stability for up to 8 hours.⁸

After confirmation of catheter placement by CT the morning after surgery, the total amount of G207, as defined by each patient's dose level, was delivered in a total volume of 2.4 mL administered in up to 4 catheters. Each dose portion was infused via a separate syringe mounted in a microprocessor-controlled infusion pump for a total infusion rate of 0.4 mL per hour over the course of 6 hours. After completion of the infusion, catheters were clamped. At least 1 hour after completion of the G207 infusion, the catheters were removed by the neurosurgeon and surgical sites were stitched at the bedside in the pediatric intensive care unit.

RESULTS

Demographics

Six patients (4 boys and 2 girls) were treated with stereotactic implantation of catheters and infusion of HSV G207 since October 2016. Age at time of catheter implantation ranged from 10—18 years (average 13.8 years). There were 5 patients with glioblastoma and 1 with anaplastic astrocytoma (Table 1). Tumor locations included frontal lobe, temporal lobe, parietal lobe, occipital lobe, insula, and thalamus. Preoperative MRI and postoperative CT scans and subsequent MRI scans were available and reviewed for all 6 patients.

Catheter Placement Accuracy

In 6 patients, a total of 22 catheters were placed into areas of recurrent high grade supratentorial tumor. Catheters were placed into the frontal lobe, temporal lobe, parietal lobe, occipital lobe, insula, and thalamus. Ninety-six percent (21 of 22) of the catheters were placed accurately within contrast enhancing tumor mass and away from the ventricular and cisternal systems. Patient 5 required revision of 1 catheter that was in a tumor within the corpus callosum, but 2 mm from the ventricle. Given the proximity to the ventricle and cerebrospinal fluid (CSF), the catheter was withdrawn 1.5 cm at the bedside into the main body of the tumor. The CT was repeated to ensure safe tip location away from the ventricle, placement was deemed acceptable, and the standard infusion of HSV G207 was performed without incident.

Complications

There were no temporary or permanent neurologic sequelae related to placement of the catheters or to infusion of HSV G207. Patient 4 had a tract hemorrhage noted on postoperative CT scan (Figure 3). This hemorrhage did not include the catheter tip, did not cause neurologic sequelae, and was stable on follow-up MRI scan. The infusion was performed as planned through this catheter without complication. Patient 5 experienced a delayed CSF leak from the initial biopsy and catheter placement site. He presented to the emergency department 9 days after the biopsy and placement of the catheters with clear fluid drainage from the surgical site, fever to 101°F, and no other complaints. His neurologic exam was unremarkable. The leak was overseen successfully at the bedside. His white blood cell count was elevated at $13.7 \times 10^3/\text{mL}$ (normal range $3.8\text{--}9.8 \times 10^3/\mu\text{L}$) with a normal differential. A lumbar puncture was performed to rule out meningitis and the opening pressure was $>50 \text{ cm H}_2\text{O}$, with 20 mL of CSF removed to decrease pressures and for cytology. He was admitted for evaluation and had no additional fever, signs or symptoms of meningitis, or HSV encephalitis. CSF bacterial cultures were negative and HSV viral polymerase chain reaction level was found to be 5480 copies/mL (3.7 log copies/mL), consistent with residual G207 virus from the infusion (1×10^8 plaque-forming units) 8 days prior. He was discharged after bacterial infection was ruled out with no further leak. Ophthalmologic evaluation demonstrated no papilledema.

DISCUSSION

We report technical nuances and complications of catheter placement for the first clinical trial of intratumoral continuous infusion delivery of conditionally replicating HSV G207 in children. In our series of 6 children with recurrent, high grade supratentorial brain tumors, we implanted 22 catheters using a frameless stereotactic system with acceptable accuracy, and report what we believe is the first successful intratumoral catheter placement into the thalamus of a child for delivery of a novel therapeutic. Others have previously reported on the accuracy of frameless stereotactic biopsies in brain tumor patients.²³ Beyond the stereotactic accuracy of frameless stereotactic biopsies, catheters have also been placed using a frameless stereotactic system. Giese et al.²⁴ reported on the placement of 33 catheters for local brainstem chemotherapy with acceptable accuracy.

In a review of the literature,²³ errors of 0.4—6.6 mm have been described for frame-based stereotactic settings.^{25–28} In frameless systems, errors of 0.33—3.86 mm have been described.^{29–32} In a recently published study comparing both a frame-based and frameless setting for stereotactic surgery, no significant difference between both techniques was observed.³³ In line with the presented literature, the use of a frameless system for placement of catheters for the infusion of HSV G207 appears safe and efficacious.

The preliminary safety record of this procedure is comparable to reported rates for similar procedures in adults and standard stereotactically guided biopsies.^{18,19} More specifically, others have reported complication rates of 5%—7% in stereotactic neurosurgery^{34–36}; in line with our study, those referenced did not note any permanent neurologic deficits. Further, our observation of postoperative blood in only 1 of 22 placed probes falls well within the literature, further highlighting the safety of such a procedure. Next to the safety of

stereotactic biopsy acquisition in pediatric patients, others have focused on the safety of catheter placement in this patient population. Parreno et al.³⁷ reported no morbidity associated with the frameless stereotactic placement of catheters. Care was taken to avoid vascular injury in planning catheter trajectories, but tract hemorrhages may be a rare but unavoidable complication of intracranial catheter placement, especially in recurrent high-grade tumors. There is also risk of CSF leak, that can be seen with tumor biopsies and resections.³⁸ The phenomenon of an intraoperative CSF leak after durotomy may serve as a source of brain shift that may contribute to the error observed in the placement of a stereotactic catheter.³⁹

Although our patient population is well within the expected range of pediatric patients presenting with glioblastomas,⁴⁰ these patients are considerably older than the general pediatric population. Therefore, our findings must be carefully extrapolated to the general pediatric population necessitating further studies demonstrating the safety of such therapy in younger patients.

The major limitation is the single-center nature of this study. Further, the number of patients is relatively low. However, the high number of catheters placed may outweigh this limitation. Moreover, a minor complication in 6 patients (16.7%), 22 catheter placements (4.5%), and no major complications, suggest preliminarily that this is a safe procedure.

Continuous rate infusion of therapeutics through intratumoral catheters may be a promising alternative to systemic administration.⁴¹ This procedure comes with a number of potential advantages as reviewed by Vogelbaum et al.⁴² Continuous rate infusion bypasses the blood-brain barrier delivering the therapeutic directly to tumor cells, provides a mechanism to spread the therapeutic throughout the tumor by infusing through multiple catheters, and relies on a pressure gradient thus enhancing interstitial drug distribution⁴³; future studies may also seek to employ arborizing catheters thereby reducing the need to place multiple catheters within a tumor.⁴⁴ Moreover, slowly infused doses using this procedure may be lower when compared to solely diffusion-mediated delivery, thereby reducing the risk for neurologic injury.⁴³

The next phase of the current HSV G207 trial will test the safety of HSV G207 combined with a single 5 Gy of radiation within 24 hours of virus infusion, designed to enhance virus replication and an antitumor immune response.⁸ Children are a particularly promising population for oncolytic HSV-I treatment because of the lack of preexisting immunity to HSV-I; the increased expression of the primary HSV entry receptor nectin-1 (CD111), an adhesion molecule, in pediatric brain tumors; and the increased sensitivity of pediatric brain malignancies to engineered HSV (i.e., G207).^{10,21,22} In subsequent investigations, we plan to evaluate the efficacy of HSV G207 in this population and will endeavor to identify subgroups who show greater response.

CONCLUSIONS

Stereotactic placement of intratumoral catheters followed by continuous controlled rate infusion of HSV G207 appears safe and feasible in children. Future studies will determine

safety of radiation following intratumoral treatment as well as the efficacy of this approach in pediatric supratentorial malignancies.

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Drs. Markert and Gillespie are founders of and own stock and stock options (<8% interest) in Aettis, Inc., a biotech company that has licensed M032 HSV from The Board of Trustees of the University of Alabama for the University of Alabama at Birmingham and is developing other oHSVs that are not the subject of this current investigation. Dr. Gillespie currently serves as one of five unpaid members of the Board of Directors for Aettis, Inc. Dr. Gillespie is a founder of and owns stock and stock options (< 10%) in Maji Therapeutics, which is developing other HSVs that are not the subject of the current investigation. Drs. Markert and Gillespie were also founders of and owned stock and stock options (<8%) in Catherex Inc., a biotechnology company that had licensed additional intellectual property related to oHSV. Catherex, Inc., was sold to Amgen, Inc., on December 18, 2015, and they no longer participate in any decision making or have any control of any aspect of Catherex or Amgen, although they did receive proceeds from the sale of the company. Dr. Gillespie has served as a paid advisor to the Program Project at the Ohio State University that seeks to find improved methods for application of distinct oHSV to treat localized and metastatic cancers. This is generally, but not specifically, related to the subject matter of this investigation. Dr. Bernstock has equity in both CITC Ltd and Avidex Technologies.

Abbreviations and Acronyms

CSF	Cerebrospinal fluid
CT	Computed tomography
DPBS	Dulbecco's phosphate-buffered saline
HSV	Herpes simplex virus
MRI	Magnetic resonance imaging

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Figure 1.

Implantation of catheters into anaplastic astrocytoma, patient 2. **(A)** Preoperative magnetic resonance imaging (MRI), axial T1 with contrast enhancing recurrent tumor. **(B)** Postoperative computed tomography (CT), axial with similar slice to **(A)**, traversing catheters marked by arrows. **(C)** Day 4 postoperative MRI, axial T1 with contrast, demonstrating catheters within contrast enhancing tumor. **(D)** 3D reconstruction of postoperative CT scan demonstrating catheter placement within the tumor mass.

Figure 2. Implantation and biopsy procedure. (A) The stereotactic guide was used to guide a power drill to the entry site. (B) The biopsy needle was guided along the planned trajectory using the stereotactic guide and samples taken. The catheter with rigid stylet was then guided along that tract and the stylet withdrawn. (C) The catheter was tunneled subcutaneously away from the insertion site.

Figure 3.

Catheter tract hemorrhage following placement of intratumoral catheter, patient 4. **(A)** Computed tomography head, coronal reconstruction, demonstrates the hemorrhage on postoperative Day 1. **(B)** Magnetic resonance imaging, coronal T1 without contrast, on Day 4 postcatheter placement demonstrates stability of the hemorrhage. The hemorrhage was not associated with any clinical or neurologic sequelae.

Table 1.

Patient Demographics

Patient, Number	Age (years)/sex	Tumor Pathology	Tumor Location
1	12/F	Glioblastoma	Right parieto-occipital
2	18/M	Anaplastic astrocytoma	Left frontal, insular
3	14/F	Glioblastoma	Left parietal, insular
4	13/M	Glioblastoma	Mesial occipital, posterior temporal
5	11/M	Glioblastoma	Left frontal
6	10/M	Glioblastoma	Right thalamus, temporal

F, female; M, male