First-in-human evaluation of the Cleveland Multiport Catheter for convection-enhanced delivery of topotecan in recurrent high-grade glioma: results of pilot trial 1

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OBJECTIVE Progress in management of high-grade gliomas (HGGs) has been hampered by poor access of potential therapeutics to the CNS. The Cleveland Multiport Catheter (CMC), which deploys 4 independent delivery microcatheters, was developed to be a reliable, high-volume delivery device for delivery of therapeutic agents to the brain and other solid organs. The authors undertook this first-in-human clinical trial effort to evaluate the delivery characteristics of the CMC in patients with HGGs.

METHODS A series of pilot studies were launched after approval of a sponsor-investigator IND (investigational new drug) application to evaluate the delivery of topotecan and gadolinium-DTPA (Gd-DTPA) via the CMC in patients with recurrent HGG. The first pilot trial evaluated delivery into enhancing tumor and nonenhancing, tumor-infiltrated brain. Two catheters were placed with the use of a conventional frameless stereotactic technique following a biopsy to confirm tumor recurrence, and drug infusion was performed both intraoperatively and postoperatively for a total of 96 hours with the same rate for all microcatheters. Delivery was assessed by intermittent MRI.

RESULTS Three patients were enrolled in the first pilot study. MRI demonstrated delivery from all 6 catheters (24 microcatheters). The volume of distribution (Vd) of Gd-DTPA was heavily dependent upon CMC location (enhancing vs nonenhancing) with an approximately 10-fold difference in Vd observed ($p = 0.005$). There were no hemorrhages related to catheter placement or removal, and all 3 patients completed the protocol-defined treatment.

CONCLUSIONS The CMC is capable of providing backflow-resistant drug delivery to the brain and brain tumors. The volume of distribution is heavily dependent upon the integrity of the blood-brain barrier. Assessment of delivery is essential for development of loco-regionally applied therapeutics in the CNS.

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KEYWORDS glioma; topotecan; convection-enhanced delivery; surgical therapeutic; oncology; surgical technique

THE prognosis of patients with high-grade glioma (HGG) remains poor despite decades of laboratory and clinical research activities, and only incremental gains have been made. Even with the current standard treatment of maximal safe resection, fractionated radiotherapy, chemotherapy, and, most recently, external

electrical field treatment, the 2-year survival for patients with the highest grade of glioma, glioblastoma (GBM), remains only about 30%.^{8,19,23} Multiple novel approaches, many of which have shown efficacy in other cancers, have failed to provide meaningful benefit to patients with HGG. The prognosis of recurrent HGG is even more dismal, and

ABBREVIATIONS AE = adverse event; BBB = blood-brain barrier; CED = convection-enhanced delivery; CMC = Cleveland Multiport Catheter; GBM = glioblastoma; HGG = high-grade glioma; IND = investigational new drug; IRB = institutional review board; IV = intravenous; KPS = Karnofsky Performance Status; NSDU = neurological step-down unit; OR = operating room; PTFE = polytetrafluoroethylene; TMZ = temozolomide; Vd = volume of distribution.

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there are no medical treatments that have been shown to extend survival after recurrence.

One of the challenges that has hindered clinical progress is that most therapeutically active molecules are excluded from the brain, and even to a large extent from the solid, enhancing portion of brain tumors, by the blood-brain barrier (BBB). Multiple investigational approaches have attempted to overcome the BBB including drug modifications, conjugation to carriers, disruption of the BBB, intrathecal therapy, intracavitary therapy, and convection-enhanced delivery (CED). The technique of CED involves the slow, continuous infusion of therapeutics directly into tumor tissue or brain parenchyma, most often at the rate of several microliters per minute over a period of hours to days.² While preclinical models of CED have shown this to be an effective delivery technique, initial clinical use of this approach failed to show a meaningful clinical benefit for several therapeutics.^{11,18,20,25–28}

The failure of the first generation of clinical trials that used CED as a delivery method has been attributed to a number of technical and clinical trial design factors. These trials were focused mostly on the clinical evaluation of conventional and novel therapeutic molecules, and they did not take into account the limitations in the delivery technology that had been identified preclinically.¹³ At the time of these first trials, there were no specialized CED catheters; instead, readily available, largely single-lumen catheters that were designed and approved for drainage of cerebrospinal fluid were employed for this intraparenchymal delivery approach. Prior work had noted that these drainage catheters are prone to backflow of infusate around their outer surface, and additional studies showed that they were prone to blockage or plugging during insertion into the brain.¹⁰ Unfortunately, clinical investigators were not able to observe these problems in real time as, for the most part, initial trials did not involve the administration of radiolabeled drug or tracers, which would have been useful for verifying delivery. Following the failure of the only phase III trial to complete accrual, several post hoc analyses indicated that unreliable catheter placement and backflow were likely sources of poor delivery and hence lack of effect of the “delivered” therapeutic.^{18,20}

It had been previously demonstrated that a small, sub-millimeter delivery port would be less prone to backflow.¹³ It was a technical challenge, however, to create a device that would be small enough to resist backflow yet could be made rigid enough to be reliably implanted transcranially to specific locations of the brain. One approach has been to create so-called “step-down” cannulas, which are rigid and have small diameter delivery tips distally and larger diameter shafts proximally.¹⁰ This design allows these devices to be placed stereotactically to specific locations in the brain, but they can be used only intraoperatively due to the risk of injury from dislodgement or breakage in a nonsecured patient. These types of catheters have been shown to produce backflow-resistant CED, but infusions are limited to only a few milliliters of volume due to the time limitations associated with their restriction to intraoperative use only and due to their single-lumen design. Furthermore, two of these devices are restricted to intra-

operative use only, and one requires use of an intraoperative MRI, which is not a widely available resource.^{3,7}

To overcome the technical limitations associated with the “off-the-shelf” catheters used in the first generation CED trials and single-lumen catheters designed for CED, we set out to design a device that would meet the following performance criteria: 1) capable of performing reliable, high-volume (more than 10 ml) delivery into brain tumors and brain parenchyma; 2) can be left in place for days at a time; 3) constructed of materials that are biocompatible and compatible with a wide range of potential therapeutics including biologics; 4) can be placed with the use of conventional stereotactic neurosurgical techniques; 5) compatible with use in an MRI environment (although not requiring MRI for use); and 6) can be visualized with CT. The first of our devices to meet these criteria has been named the Cleveland Multiport Catheter (CMC). In this report, we describe its use in a first-in-human study that was designed to validate the delivery performance of the CMC and explore factors that may influence its use in patients with HGG.

Methods

A first-in-human pilot trial to assess the delivery characteristics of the CMC was performed under the US Food and Drug Administration’s Investigational New Drug (IND) process (Sponsor-Investigator IND application approval no. 117,240 issued to M.A.V.). This IND status covers both the investigational device and drug. This prospective, open-label, single-arm therapeutic study was approved by the Cleveland Clinic institutional review board (IRB), and all patients signed a study-specific written informed consent statement after discussion of the study with financially nonconflicted study site personnel prior to study entry. The study was registered at ClinicalTrials.gov (registration no. NCT02278510). An IRB-approved conflict of interest management plan is in place for M.A.V.

The CMC (Fig. 1) consists of a central catheter shaft, made of barium-impregnated silicone, that houses 4 independent infusion microcatheters, which are made of polytetrafluoroethylene (PTFE). The diameter of the central shaft of the CMC is 2.5 mm, and the outer diameter of each microcatheter is 0.38 mm. The microcatheters are each connected to a Luer connector, and there is no interruption in the infusion path from the Luer connector to the distal tip of the microcatheter. The distal tips of the microcatheters are withdrawn into the central CMC shaft when the stylet is in place, and they deploy radially when the stylet is removed. Initial development of the CMC was performed at the Cleveland Clinic, and the clinical version of the CMC was developed jointly by the Cleveland Clinic and Parker Hannifin Corp. M.A.V. is co-inventor of the CMC.

The primary objectives of the study were to investigate by MRI the spatial and temporal distribution of topotecan and Gd-DTPA in tumor and tumor-infiltrated brain when administered by CED with use of the CMC, the influence of rate and topotecan concentration on distribution, and the impact of delivery location on distribution. Secondary objectives included evaluation of backflow, safety, toler-

FIG. 1. Illustration of the Cleveland Multiport Catheter in the (**upper**) undeployed state, and (**lower**) with its microcatheters deployed. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2013–2017. All rights reserved.

ability and toxicity of topotecan, and activity of single-agent topotecan.

Inclusion and Exclusion Criteria

To qualify for inclusion, patients had to meet the following criteria: 1) histologically confirmed WHO grade III or IV glioma (high-grade glioma [HGG]), 2) previous biopsy or resection followed by adjuvant radiation and chemotherapy, 3) evidence of recurrence or progression based upon imaging, and 4) indication for a stereotactic biopsy for confirmation of recurrence or progression. Patients were also required to be at least 18 years of age and have a KPS of 70–100. The volume of the enhancing component of the recurrent tumor was required to be less than 40 cm³ and patients were required to have laboratory values permissive for surgery and MRI with a contrast agent. Exclusion criteria included diffuse or subependymal disease, pregnancy, tumors in the posterior fossa, enhancing tumor in both hemispheres, active infection, and radiation or chemotherapy within 4 weeks of enrollment.

Surgical Procedure

Enrolled patients underwent a clinically indicated stereotactic biopsy under general, endotracheal anesthesia. Brainlab iPlan was used for entry point/target planning and intraoperative stereotactic guidance. Once the intraoperative diagnosis was confirmed to be recurrent high-grade glioma, 2 CMC catheters were placed with use of stereotactic guidance in a manner similar to the biopsy itself. One CMC was placed into enhancing tumor via the same burr/twist drill hole and trajectory as the biopsy, and the second was placed into tumor-infiltrated brain surrounding the enhancing mass via a separate incision and burr/twist drill hole.

While certain details of the surgical procedure evolved over the course of the first 3 cases, the general approach

remained the same. Each of the planned entry points was localized, and an incision was made over each area. Following hemostasis, either a 9-mm burr hole or a 3-mm twist drill hole was made. For the first case we made burr holes, but for the second two we used a twist drill approach, which is our standard technique for stereotactic procedures, including stereotactic biopsy. Following cranial access, stereotactic measurements were made with use of the image guidance system from the top of the guide tube that was secured in a guide arm (UniArm for 2 cases, Varioguide for 1 case). The CMC devices have 1-cm markings on their shaft, and we used a permanent marker to mark the final distance prior to catheter placement. Each CMC contains 4 independent microcatheters (Fig. 1), and prior to placement the CMC microcatheters were primed with the sterile 5-mM Gd-DTPA solution via stopcocks (2 cases) or self-sealing Luer connectors (1 case) at the proximal end of each microcatheter. The rigid CMC stylet was placed via a dedicated, noncommunicating central channel, which resulted in withdrawal of the microcatheters into the central body of the catheter. The dura mater was perforated with use of a Kelly monopolar cautery probe and electrocautery, and then each CMC device was advanced to its preplanned depth. Once the CMC was at the marked depth, the stylet was disengaged from the CMC hub and the hub was advanced toward the patient in the process of deploying the microcatheters into tumor or tumor-infiltrated brain tissue. The stylet was removed along with the guidance apparatus, with the CMC shaft being secured with forceps at the scalp surface. Sutures were placed to close the galea and then the skin surface around the catheter shaft for the first case in which a longer incision was made to create burr holes. For the other 2 cases, in which only a stab wound incision was made, 1 or 2 full-thickness sutures were placed to close the incision around each catheter. Each catheter-securing device was advanced to the scalp and secured to the skin, and the catheters were secured to the “ramp” portion of the securing device (Fig. 2). The surgical drapes were removed and the patient was removed from the head clamp.

The surgeries were performed in an operating room (OR) equipped with an IMRIS intraoperative MRI, and noncontrast imaging was performed to confirm accurate placement of each CMC and to evaluate for immediate surgical complications. Once the MRI was completed, the MR scanner was left in place over the patient and each stopcock or self-sealing Luer was attached to its own infusion line, which was served by its own MedFusion 3500 pump programmed with the infusion parameters noted below. Intraoperative infusion was performed for 2 hours, and intermittent MRI (without a intravenous [IV] contrast agent) was performed during the infusions. The infusions were then stopped, the infusion lines were clamped and the syringes were removed from the pumps and secured to the patients. The MR scanner was removed from the OR and the patient was reversed from anesthesia, extubated, monitored in the post-anesthesia recovery unit, and once deemed stable transferred to the neurological step-down unit (NSDU). In the NSDU, the syringes were reconnected to the pumps, tubing clamps removed, and the infusions were continued as per protocol, for a total of 96 hours.

FIG. 2. Upper: Photograph of the “ramp” accessory used to secure the CMC in place. Lower: Photograph of the CMC within the “ramp” accessory.

Patients were maintained on prophylactic antibiotics until the devices were removed.

During the infusions, the patients were taken each day for a noncontrast MRI. For these studies, the infusion lines were clamped, and the syringes removed from the pumps and secured to the patient. Imaging consisted of MPRAGE and T2 volumetric sequences. Following the completion of imaging, the patients were returned to the NSDU and the infusions were resumed. At the end of the 96-hour infusion, the infusion lines were removed from the CMCs prior to a final MRI. After the MRI was completed, the CMCs were removed at bedside and a single suture was used at each site to close the wounds. Patients were observed for an additional 24 hours in the NSDU prior to transfer to the regular nursing floor, or discharged, as clinically indicated.

The study design called for 4 cohorts of patients to be evaluated in a 3+3 design. The infusion parameters for the first cohort were based upon those specified in Bruce et al.⁴ Specifically, we started with the parameters used for the maximal tolerated dose (MTD) minus 1 cohort (i.e., the dose and infusion parameters that were evaluated in one cohort below those found to be safe and 2 cohorts

below those found to be toxic in the Bruce et al. study). The Bruce et al. study had used 2 single-lumen catheters placed intratumorally; we used the same total dose and infusion time and equally divided the infusate volume for each catheter used in the Bruce et al. study between the 4 microcatheters for each CMC. Hence the infusion rate per microcatheter was one-fourth of that used per catheter in the Bruce et al. study. The infusion parameters were as follows: concentration of topotecan was 0.067 mg/ml, concentration of Gd-DTPA was 5 mM, total infusion volume was 38 ml (19 ml per CMC), total infusion duration was 96 hours, total infusion rate was 0.396 ml/hr or 6.6 μ l/minute, and hence the infusion rate per microcatheter was 0.825 μ l/minute.

Evaluation of the primary endpoint (volume of distribution [Vd]) was performed by an independent third party (ImageIQ, Inc.) who was blinded to the infusion protocol and clinical results. Volume of distribution of the Gd-DTPA, which was a surrogate for topotecan, was determined from the MRI studies performed during and at the end of infusion. Analysis of contrast agent volume and concentration across longitudinal MPRAGE MRI sequences was performed using customized, automated algorithms written in MATLAB (v2011b; MathWorks) in conjunction with ImageIQ registration and visualization libraries. Briefly, longitudinal MPRAGE sequences for a given subject were coregistered using a mutual information algorithm. Bolus centroids (x, y, and z coordinates) were defined for each gadolinium pool visible in the first time point for a given subject and subsequently used as seed points for a 3D region growing algorithm applied to each registered temporal series for that subject. Following the application of morphological filters and deletion masks for the removal of gadolinium contribution from surrounding sulci, the resulting contrast mask for a given time point consisted of segmented gadolinium pools surrounding each seed point and extending to adjacent borders with nonperfused tissue (≤ 200 gray level determined from an average tissue intensity across all volumes). Lastly, to determine the relative concentration and distribution of contrast agent in each segmented bolus, volumes were calculated for contrast intensities ranging from 200 to 1000 gray-levels (50 gray-level histogram bins) with each gray-level bin represented by a specific heat-map value in a pseudo-colored 3D representation of the contrast bolus. To validate effectiveness of the algorithm in segmenting contrast, 3D volumes of the contrast, corresponding intensity heat-maps, and original 3D MRI sequences were visualized in ImageIQ's 3D-rendering software using various opacity and isosurface representations. We performed a t-test to compare the volumes of distribution within enhancing versus nonenhancing tumor. This analysis was performed with use of R Statistical Programming Environment (version 3.4.1).

Safety was evaluated with the use of CTCAE v4.0. While the primary analysis was focused on the safety of the CMC device, we also recognized that there also was risk associated with the device implantation procedure and with the drug combination itself (topotecan and Gd-DTPA). We sought to identify the source of any adverse events (AEs) based upon a reasonable likelihood of causality, and these events and the final assigned causality were determined by

investigators who did not have financial conflicts of interest (C.B. together with A.M.M., D.M.P., and M.S.A.).

Results

Demographics and Prior Treatments

Three patients were treated in this pilot study between December 2014 and February 2015. All 3 were male, and their ages ranged from 20 to 59 years of age. Two had the original diagnosis of GBM and one had the original diagnosis of anaplastic astrocytoma. All tumors were in the right frontal lobe. At the time of original diagnosis, one had a prior biopsy only, one had a subtotal resection of their enhancing mass, and one had a complete resection of their enhancing mass. All 3 had been treated with prior fractionated radiotherapy and temozolomide (TMZ) chemotherapy as well as a median of 3 cycles of adjuvant TMZ (range 1–13 months). Other prior treatments included the rindopepimut vaccine for 1 patient, lomustine followed by etoposide for 1 patient, and bevacizumab followed by lomustine followed by etoposide for 1 patient. At the time of enrollment on this study, 1 patient had a Karnofsky Performance Status (KPS) of 80 and 2 had KPS of 90. These data are shown in Table 1.

Surgical Procedure and Intraoperative Infusions

After induction of general anesthesia and positioning in our IMRIS OR, all 3 patients underwent an initial image-guided stereotactic biopsy of their residual/recurrent enhancing mass. The frozen-section diagnosis for all 3 patients was GBM. Two CMC devices were placed for each patient as described above, and all were placed via a single pass without difficulty. Following postplacement MRI, all of the microcatheters were connected to their syringe pumps while the patients remained in the intraoperative MRI, with the pumps secured outside of the 5 Gauss line. All patients completed the 2-hour intraoperative infusion without difficulty. Intermittent imaging was performed every 30 minutes. After the completion of the 2-hour infusion, the MRI was removed, and all patients were reversed from anesthesia without difficulty. There were no new neurological deficits or intraoperative complications.

Perioperative Infusions

All 3 patients completed the full 96 hours of infusion. MRIs were completed at the end of each day and following the completion of the infusions before removal of the CMC devices. There was one event of a CMC Luer connector failure on one of the microcatheters for the first patient. This occurred when the patient was being transferred from the MRI scanner at the end of the first day of treatment and the 3-way stopcocks attached to each Luer connector got tangled, resulting in an unexpectedly high force on the Luer-microcatheter joint. This disconnection was immediately recognized and the proximal end of the microcatheter was clamped and occluded with a sterile dressing. The MRI that had been done just prior to the disconnection showed that it had produced effective delivery of the infusate. The remaining infusion volume was redivided among the remaining 7 microcatheters to permit the patient to complete the full infusion in the 96-hour

TABLE 1. Patient characteristics

Characteristic	Patient 1	Patient 2	Patient 3
Age (yrs)	20	59	38
Sex	Male	Male	Male
Initial diagnosis	GBM	GBM	AA
Tumor location	Rt frontal lobe	Rt frontal lobe	Rt frontal lobe
Initial surgical procedure	Resection	Biopsy	Resection
Duration of adjuvant TMZ therapy	13 cycles	3 cycles	1 cycle
No. of subsequent treatments	1	2	3
KPS at enrollment	90	80	90

AA = anaplastic astrocytoma.

period. There were no clinical manifestations associated with this event. For the next two patients, an accessory module was created to secure the Luer connectors to the hub, thereby eliminating the possibility of tangling and unintended strain to the Luer-microcatheter connection, and there were no further events of Luer disconnection.

For patient 1, we changed the syringes on a daily basis at the request of our research pharmacy, despite preclinical data that we had submitted as part of our IND that showed stability of the topotecan/Gd-DTPA mixture for up to 128 hours. Despite the use of careful technique for performing the syringe swaps, we observed on subsequent MRIs the presence of air introduced into the system. Once made aware of this issue, the research pharmacy permitted us to use a single syringe per microcatheter for 96 hours for patients 2 and 3, and we did not observe any further issues relating to the introduction of air into the brain parenchyma.

Following removal of the CMCs, all 3 of the patients were discharged from the hospital a median of 2 days (1–3) later.

Volumes of Distribution

Monitoring of the intraoperative infusions with MRI showed variable results. Because of the low infusion rates (0.0825 μ l per minute), only about 10 μ l were infused per microcatheter during the intraoperative infusions. Figure 3 shows the variable results observed, and these were difficult to quantify because of their small volumes. There was no evidence of backflow around the CMC shafts. Leakage of contrast into sulci was observed to be associated with the locations of some microcatheters, but this did not appear to impact on the overall volumes of distribution. Ultimately, these intraoperative imaging results were not indicative of the perioperative infusion volumes of distribution.

The maximum volumes of distribution (Vds) observed with perioperative infusion up to 96 hours are shown in Table 2. We separately analyzed the Vds for the intratumoral (enhancing tumor, ET) and peritumoral (nonenhancing tumor, NET) CMCs for patients 2 and 3; we could not separately identify these 2 volumes for patient 1 due to

FIG. 3. Axial MPRAGE MR images showing the progress of the intraoperative CED infusions. Gd-DTPA was co-administered with topotecan by CED. No IV contrast agent was administered. ET = enhancing tumor; NET = nonenhancing tumor.

the close proximity of the 2 CMCs in his case. There were obvious differences in the Vd for CMCs placed into tumor-infiltrated brain (NET) versus solid tumor (ET) (Fig. 4). The maximum Vd for the CMCs placed in tumor-infiltrated brain was 19.4 cm³, whereas for the CMCs placed in enhancing tumor it was 1.7 cm³ ($p = 0.005$). The relationship

between the Vd and duration of infusion was variable (Fig. 5). In 2 patients, the Vd of the CMC in tumor-infiltrated brain peaked at 48 or 72 hours and then declined, and in 1 patient it continued to increase until 96 hours. The early peak and subsequent decline was not associated with backflow or leakage into a CSF space; instead there was a diffuse reduction in the intensity of contrast suggestive of an overall increase in the rate of efflux from the brain of the Gd-DTPA.

Adverse Events

Aside from the 1 Luer disconnection described above, which had no clinical manifestation, there were no other device-related AEs. There were no occurrences of infection or intracranial hemorrhage.

TABLE 2. Maximum volumes of distribution

Variable	Patient 1	Patient 2	Patient 3
Vd (ET)	—*	1.7 cm ³	1.4 cm ³
Vd (NET)	18.8 cm ³	19.4 cm ³	15.6 cm ³

ET = enhancing tumor; NET = nonenhancing tumor.

* For patient 1, the Vds for the 2 CMCs could not be visualized separately.

FIG. 4. Axial MPRAGE MR images showing the peak Vd for each patient. Images are centered on the catheters placed in enhancing tumor (ET) or nonenhancing tumor (NET). For patient 1, the Vds for the 2 CMCs overlapped and so only 1 image is shown.

FIG. 5. Graphs showing the change in Vd over the course of the 4-day infusions. **Upper:** CMC placed in nonenhancing tumor. **Lower:** CMC placed in enhancing tumor.

TABLE 3. Adverse events during infusions

Event	Patient 1	Patient 2	Patient 3
Memory impairment		Grade 2	
Urinary incontinence		Grade 2	
Fatigue		Grade 1	
Slow gait		Grade 2	
Muscle weakness		Grade 2	Grade 3
Inability to perform ADLs			Grade 3
Total number of events	0	5	2

ADL = activities of daily living.

All events were considered to be unrelated to study drugs or procedures and resolved to baseline with medical treatment (e.g., adjustment of steroids, physical therapy).

Clinical AEs are shown in Table 3. Overall, the infusions were well tolerated. There were no AEs related to the catheter implantations. Patient 1 had no AEs during the infusions. Patients 2 and 3 had AEs during the infusions that were not considered to be related to the study agents or infusions themselves.

Clinical Follow-Up

While this was not an efficacy-oriented study, we did collect radiological and clinical follow-up data on these patients. Patient 1 developed radiographic progression at 60 weeks and survived a total of 93 weeks after treatment on this protocol. Patients 2 and 3 developed rapid progression of their enhancing disease, which had not been completely treated with use of the prespecified infusion parameters. Patient 2 had further progression of the enhancing tumor and underwent an uncomplicated craniotomy for subtotal tumor debulking 1 month after the CED treatment. His tumor continued to progress and his neurological status declined. He died 4 months after protocol treatment. Patient 3 had progression of his enhancing tumor 1 month after the CED treatment and treatment with metronomic temozolomide was initiated. His tumor continued to progress, his neurological condition continued to decline, and he died 3 months after treatment. As it became obvious that the infusion parameters that were being used for the delivery into enhancing tumor were insufficient to overcome the rapid efflux of tracer, and presumably drug, across the defective BBB that exists in enhancing tumor, we terminated enrollment to this protocol and instead initiated a pilot study of peritumoral delivery only following resection of the enhancing mass. The results of the second pilot study (NCT2500459), which is ongoing, will be the subject of a separate report. We have also opened a third pilot study to evaluate the impact of infusion rate escalation on volume of distribution in unresected, enhancing tumor (NCT3193463).

Discussion

A wide range of conventional and novel, targeted therapeutics for HGG have been shown to be effective against HGG in vitro or in preclinical models that recapitulate only the enhancing portion of HGG. Clinical failure of nearly

all of these compounds can be traced to the fact that these therapeutics are largely excluded from the brain, most particularly in non-contrast-enhancing areas of tumor infiltration.^{22,24} CED provides a method by which to introduce therapeutics directly into tumor-infiltrated brain and into enhancing brain tumors. However, expectations of clinical success hinge on the ability of CED to actually deliver. The failure of the first generation of CED trials has been linked to the lack of reliable delivery technology, and it is quite likely that the therapeutics in these trials never achieved sufficient concentrations at the targeted sites of disease.

We set out to validate the clinical performance of a novel device that was designed specifically to achieve high-volume CED and evaluate factors influencing its ability to achieve high volume and reliable delivery. Our initial experience with this device showed that it could be placed into brain or brain tumor successfully with use of conventional stereotactic neurosurgical techniques and left in place for days while the infusions continued, up to 96 hours in total duration. As had been the case in many of the prior trials involving CED, the patients tolerated the infusions well and all 3 completed the infusion procedure as expected. The one event of a Luer connection breakage was due to unintended strain on this bond, and it reflects the known difficulty of bonding PTFE to other materials. Rapid design and adoption of a strain-relief device appears to have resolved this issue, and there were no further problems with disconnection (i.e., no problem with disconnection in 23 of 24 microcatheters).

Use of a co-infused imaging tracer was a critical element to our validation of delivery and evaluation of factors influencing Vd. Prior preclinical and limited clinical studies had demonstrated the safety and utility of tracers for CED; yet, these were not used in most of the first generation of CED trials due to resistance from regulatory bodies.^{1,5,6,9,14–17,21,29} The limited experience with a co-infused tracer that occurred during development of cintredekin besudotox demonstrated the unreliability of the single-lumen, “off-the-shelf” catheter used in the phase III trial of that drug and it provided evidence in support of the hypothesis that therapeutic failure was, at least in part, due to failure of delivery.²⁰ With the use of a continuously infused tracer we were able to evaluate therapeutic delivery over the entire course of treatment, and this approach is in contradistinction to one in which a limited amount of tracer is infused prior to infusion of the therapeutic. With our approach we were able to observe that the Vd varied over time and it appeared that the infusate may have had an impact on the efflux rate of the tracer in some cases. As we are still in the early stages of drug development in the field of CED, it will be important to understand how drugs infused directly into the brain may impact on the integrity of the BBB and influence pharmacokinetics.

The most salient observation we made with the use of a tracer is that Vd of our infusate was dependent upon location of the CMC. The Vd in nonenhancing, tumor-infiltrated brain was consistently substantially larger than that observed in enhancing tumor. This is not an unexpected result, and the issue of therapeutic target (enhancing vs nonenhancing tumor) has been discussed in prior reports.¹² We believe that the differences in Vd between enhancing

and nonenhancing CMC locations is related to the higher rate of efflux that occurs in enhancing tissue. Our first protocol did not permit infusion rate escalations, which likely would overcome the higher rate of efflux, and an infusion rate escalation approach will be the subject of a future study. By way of comparison, the infusion rate per microcatheter in this study (0.825 $\mu\text{L}/\text{minute}$) is at least 1 order of magnitude slower than those used in other studies involving delivery into enhancing tumor. We are in the process of more completely exploring the impact of infusion rate on the performance of the CMC in enhancing tumor in a separate pilot trial (NCT3193463). On the other hand, the relatively large, and to some degree, unprecedented volumes of distribution within nonenhancing tumor-infiltrated brain demonstrate the capability of the CMC to deliver infusates and also validate the concept that multiday infusion is likely to be superior to intraoperative-only infusion when performed with use of a stereotactically implanted catheter that cannot be used outside of the OR.

One area of controversy relates to the question of how effectively a tracer indicates the actual distribution of the therapeutic molecule being delivered. On the one hand, use of tracers has the benefit of indicating more generally whether there is forward flow, as opposed to backflow. That said, it is important in the development of therapeutics to have some indicator of actual drug distribution and, even more so, the pharmacokinetics of the delivered agent. There is some degree of controversy regarding the appropriate physical properties of a tracer. Some prior work has shown that tracers for CED work best when they are relatively matched in size to the therapeutic molecule they are tracing.¹⁵ Other investigators have found that distribution of some large molecules can be effectively tracked with a relatively smaller tracer.²¹ For this study, topotecan (MW 457 g/mol) and Gd-DTPA (MW 938 g/mol) are reasonably well matched in size, and so we have reason to believe that the Vd of Gd-DTPA was a plausible surrogate for the distribution of topotecan. However, matching size alone is not enough to be certain of the fidelity of the tracer, as other chemical properties may affect how easily a therapeutic compound spreads within tumor or brain tissue. Another approach would be to directly label the drug itself and then image its distribution; this approach also has limitations with regard to how the label may alter the chemistry of the parent compound, and it introduces additional regulatory hurdles to overcome. Ultimately, questions regarding the stability of a therapeutic compound in tissue over time also will impact on the utility of a tracer, as distribution of a drug that has been rendered ineffective by local tissue properties likely will have the same impact as lack of distribution. Nonetheless, tracers will be a valuable tool for assessing the results of treatment over the course of the disease, and we will be able to use the MR images obtained during infusion to evaluate whether recurrences are likely to be within the field of prior treatment (therapeutic failure) or outside of the region treated (new therapeutic target).

Conclusions

We have demonstrated that the Cleveland Multiport

Catheter (CMC) can be placed safely into targets within the brain with the use of conventional neurosurgical stereotactic techniques and equipment. Furthermore, the CMC was used to successfully deliver therapeutics in the OR, within the MRI environment, and for several days outside of the OR. Finally, we have shown that it is essential to monitor therapeutic delivery in real time, with the use of a co-infused tracer or other related technology, as the tissue characteristics of the infusion target will have a meaningful impact on the volume of distribution of the infused therapeutic.

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Conception and design: Vogelbaum, Ahluwalia. Acquisition of data: Vogelbaum, Brewer, Mohammadi. Analysis and interpretation of data: Vogelbaum, Mohammadi, Peereboom, Ahluwalia. Drafting the article: Vogelbaum. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Vogelbaum. Administrative/technical/material support: all authors. Study supervision: Vogelbaum.

Supplemental Information

Previous Presentations

Portions of this work were presented in abstract form at the Society for NeuroOncology 2015 Annual Meeting.

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