Magnetic Resonance Imaging–Based Assessment of Gadolinium-Conjugated Diethylenetriamine Penta-Acetic Acid Test-Infusion in Detecting Dysfunction of Convection-Enhanced Delivery Catheters

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BACKGROUND: **In a phase 1 trial conducted at our institute, convection-enhanced delivery (CED) was used to administrate the Delta-24-RGD adenovirus in patients with a recurrent glioblastoma multiforme. Infusion of the virus was preceded by a gadolinium-conjugated diethylenetriamine penta-acetic acid (Gd-DTPA) test-infusion. In the present study, we analyzed the results of Gd-DTPA test infusion through 50 catheters.**

METHODS: **Thirteen adults with a recurrent glioblastoma multiforme were enrolled in a larger phase 1 multicenter, dose-finding study, in which a conditionally replication-competent adenovirus was administered by CED. Up to 4 infusion catheters per patient were placed intra- and/or peritumorally. Before infusion of the virus, a Gd-DTPA infusion was performed for 6 hours, directly followed by a MRI scan. The MRIs were evaluated for catheter position, Gd-DTPA distribution outcome, and contrast leakage.**

RESULTS: **Leakage of Gd-DTPA into the cerebrospinal fluid was detected in 17 of the 50 catheters (34%). Sulcus crossing was the most frequent cause of leakage. In 8 cases, leakage could only be detected on the fluid-attenuated inversion recovery sequence. Nonleaking catheters showed a significantly larger Gd-DTPA distribution fraction (volume of distribution/volume of infusion) than leaking catheters ($P = 0.009$). A significantly lower volume of distribution/volume of infusion was observed in intratumoral catheters, compared with peritumoral catheters ($P = 0.004$). Gd-DTPA test infusion did not result in significant changes in Karnofsky Performance Score and Neurological Status.**

CONCLUSIONS: **Pre-CED treatment infusion of Gd-DTPA is an adequate and safe method to identify dysfunctional catheters. The use of an optimized drug delivery catheter is necessary to reduce leakage and improve the efficacy of intracerebral drug infusion.**

INTRODUCTION

Delivery of therapeutic agents into the brain has been an ongoing challenge for many years. The systemic delivery of drugs to the brain is limited by the presence of the blood–brain barrier, which only allows the selective entrance of molecules on the basis of size, solubility, and electrical charge. To circumvent the blood–brain barrier, more direct approaches to the brain parenchyma and cerebrospinal fluid (CSF) have been explored. Many of these techniques depend on the potential of the therapeutic agent to diffuse into the brain tissue, which results in a very limited area of distribution up to a few millimeters. Other challenges encountered in diffusion-based delivery techniques are how to selectively direct the agents to the target region and how to maintain constant and pharmacologically effective drug concentrations at the desired site in the brain. Clinical attempts to deliver potentially promising drugs have thus far been disappointing as the result of poor drug efficacy and serious side effects.[1]

Key words
- Brain
- Convection-enhanced delivery
- Drug-delivery system
- MRI test infusion

Abbreviations and Acronyms
CED: Convection-enhanced delivery
CSF: Cerebrospinal fluid
CT: Computed tomography
FLAIR: Fluid-attenuated inversion recovery
GBM: Glioblastoma multiforme
Gd-DTPA: Gadolinium-conjugated diethylenetriamine penta-acetic acid
MRI: Magnetic resonance imaging
Vd: Volume of distribution
Vi: Volume of infusion

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Citation: World Neurosurg. (2016) 89:272-279.
http://dx.doi.org/10.1016/j.wneu.2016.02.003

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

In contrast to techniques that rely on diffusion, convection-enhanced delivery (CED) uses a constant pressure gradient, rather than a concentration gradient, established at the tip of an infusion catheter by a pump creating a bulk flow, which pushes the drug into the extracellular space. CED allows the distribution of therapeutic agents, like small molecules, macromolecules, and also larger particles such as viral vectors, into the brain in relatively large volumes with a steep concentration drop at the advancing margin of the bulk flow.[2]

In a phase 1 trial conducted at our institute, CED was used to deliver the Delta-24-RGD adenovirus, a genetically engineered conditionally replication-competent virus, in patients with recurrent glioblastoma multiforme (GBM). Visualizing infusions in real-time has proven to be an essential component of CED trials, allowing minimization of inappropriate infusion, such as leakage to the CSF spaces and thus reduction of the potential for adverse effects.[3] Because strict safety requirements did not allow for real-time monitoring in this trial, virus-infusion was preceded by a test-infusion of gadolinium-conjugated diethylenetriamine pentaacetic acid (Gd-DTPA).

In this study, we evaluated whether the infusion of Gd-DTPA before the start of the drug infusion could provide sufficient information on CED catheter function. Therefore, we studied which magnetic resonance imaging (MRI) sequences could be used best to evaluate low concentrations of Gd-DTPA in tumor, brain tissue, and CSF. Furthermore we analyzed the results of gadolinium test-infusion through 50 catheters in a human clinical trial.

MATERIALS AND METHODS

Patients and Treatment

Patients in this study were enrolled in the dose-escalation part of a larger phase 1 multicenter, dose-finding trial, in which a conditionally replication-competent adenovirus (DELTA-24-RGD) is administered by CED to patients with recurrent GBM. The trial was registered at http://clinicaltrials.gov (NCT01582516). Between June 2010 and October 2012, 13 adults with a recurrence of a histologically proven GBM and a Karnofsky performance status rating $\geq$70% were enrolled at the Erasmus MC—University Medical Center Rotterdam, Netherlands. Criteria for catheter placement were unifocal recurrent tumor, restricted to one hemisphere, without a midline shift $>$0.5 cm or radiologic signs of uncal herniation. Then, patients meeting the inclusion criteria who had a recurrent tumor not amenable for surgical resection underwent 1 surgical procedure in which a needle biopsy of the tumor was performed and up to 4 infusion catheters were placed by the use of neuronavigational guided surgical techniques. Three patients with tumors accessible for surgery underwent surgical resection first, in a separate operative procedure.

Before infusion of the virus via CED, a test infusion with Gd-DTPA was performed. Delta-24-RGD virus infusion was started on the day after conclusion of the test-infusion with the use of those catheters that did not show apparent leakage into CSF compartments. Follow-up MRIs (with and without intravenous contrast agent) were obtained at 12 weeks and every 3 months after virus infusion. Optional assessment for inflammatory brain reaction by MRI was obtained within 3 weeks after infusion. Informed consent was obtained from all patients, and the study was approved by the Institutional Review Board and the Central Committee on Research Involving Human Subjects of the Netherlands.

Imaging and Gadolinium Test-Infusion

All patients underwent MRI (high-resolution T1-weighted with and without intravenous contrast, T2-weighted imaging, diffusion tensor imaging, and fluid-attenuated inversion recovery (FLAIR) imaging, slices $\leq$3 mm) within 1 week before catheter placement. These images were used to plan the targets and trajectories of 4 CED catheters. To confirm proper catheter placement, a noncontrast computed tomography (CT) scan using slices $\leq$3 mm was performed immediately after catheter placement followed by a Gd-DTPA (Magnevist; Bayer Schering Pharma, Berlin, Germany) infusion at 0.2—0.3 mL/h for 6 hours at a concentration of 1 mmol/L. To assess proper convective function of the placed catheters and to identify possible leakage of Gd-DTPA into the subarachnoid or ventricular CSF space, MRIs (high-resolution T1-weighted without intravenous contrast, T2-weighted imaging, diffusion tensor imaging, and FLAIR imaging, slices $\leq$3 mm) were obtained directly after conclusion of Gd-DTPA infusion.

Catheter Planning and Placement

The surgical planning procedure for the infusion catheters was performed on the basis of postresection MRI for patients who underwent tumor debulking or the MRI scan performed before catheter placement for patients not amenable for surgical resection using iPlan Flow (Brainlab AG, Feldkirchen, Germany), a neurosurgical planning software tool, which has been described in detail previously.[3-5] Depending on tumor size and geometry, 4 trajectories peritumoral and/or intratumoral were generated on the basis of previously developed catheter placement guidelines.[3] In this study, criteria for catheter placement were defined as follows:

1. The distal ending of the catheter must be surrounded by solid tissue over a trajectory length of at least 2.5 cm; this part may not transverse sulci or other CSF cavities.
2. Catheter tips must be at least 0.5 cm away from ventricular system.
3. Catheter tips must be separated from the resection cavity over a distance of at least 1.0 cm.
4. Catheter tips must be separated from each other over a distance of at least 1.0 cm.

In addition, catheter tips needed to be planned into solid tumor mass and/or into infiltrated area of brain surrounding the solid tumor mass as determined by presence of edema.

Surface facial landmarks or fiducial markers were the basis for registration of the patient's head and subsequent matching with the image volume. Insertion of the catheters following the planned trajectories was performed with a Kolibri Navigation System (Brainlab AG) in the operating room with the patient receiving general anesthesia. For sterile frameless insertion of the catheters, the VarioGuide system (Brainlab AG), a rigidly mounted holding device, was used. After the stylet was removed under constant irrigation, catheters were tunneled subcutaneously over a distance