**Editorial**

**Convection-enhanced delivery for diffuse intrinsic pontine glioma**

MARK M. SOUWEIDANE, M.D.

Department of Neurological Surgery, Weill Cornell Medical College; and Memorial Sloan-Kettering Cancer Center, New York, New York

In 2002 our laboratory published the first experience with using convection-enhanced delivery (CED) in the brainstem as a potential therapy for children with diffuse intrinsic pontine gliomas (DIPGs). Since then, the strategy has been aggressively investigated and has recently been integrated into the clinical arena. There are 2 current clinical trials in the United States specifically designed for using CED in children with DIPG (ClinicalTrials.gov nos. NCT00880061 and NCT01502917). A major obstacle to the widespread implementation of CED for brain tumors has been the absence of a reliable method for determining drug distribution. With their current article, “Magnetic resonance imaging properties of convective delivery in diffuse intrinsic pontine gliomas,” Dr. Lonser and colleagues have contributed invaluable information that will undoubtedly provide a foundation in the design of future clinical trials employing CED.

As part of a Phase I clinical trial using CED to deliver the targeted compound interleukin-13–Pseudomonas exotoxin (IL13-PE), distribution was monitored by coinfusion with the surrogate tracer Gd-DTPA. This work is profound in that it offers more than anecdotal evidence that Gd-DTPA, coadministered via local delivery, can be used to detect distribution using an in vivo methodology in humans. Additionally, the reported volumes and patterns of distribution provide further clarity of infusion parameters (volume of distribution/volume of infusion [Vd/Vi] ratio and infusion rate) that should be employed when using CED in the brainstem of children with DIPG. The paper also provides convincing information that the concentration of Gd-DPTA is important for a more reliable estimate of Vd.

The conceptual backbone of CED is a major departure from systemic chemotherapeutic strategies in that CED will undoubtedly result in intratumoral variability in chemotherapeutic concentrations. Furthermore, tumor morphology that does not conform to a sphere, variations in fiber tract orientation, presence or absence of tumor cystic degeneration, and proximity of ependymal or pial interfaces are all features that have been shown to alter distribution with CED. Consequently, it is unlikely that the entire tumor volume of an invasive glioma will be exposed to equal concentrations of agents delivered via CED. In fact, it is likely that trials thus far conducted in patients with fibrillary astrocytoma have failed to adequately encompass the entire intended treatment volume. Without knowing where therapeutic compounds are being distributed and in what concentration, any hope of determining therapeutic efficacy is impossible. If the administered agent is not reaching the tumor volume, it is shortsighted to believe therapeutic efficacy is possible. Much like stereotactic radiotherapy, regional therapy demands validation of dose in a three-dimensional environment. The authors have definitively shown that in vivo monitoring of distribution is possible. Coinfusion of Gd-DTPA during CED provides a critical and basic methodological step forward in neurooncology, confirming overlap of treatment volume with tumor burden.

While coinfusion with Gd-DTPA is a promising avenue that provides a first step in determining the pharmacokinetics of direct drug delivery, further clarification will be helpful. Surrogate tracers have an inherent potential to misrepresent the actual distribution of the therapeutic compound due to differences between the physical properties of the tracer and the therapeutic compound. With an ever-expanding arsenal of therapeutic compounds with widely variable physical and biochemical properties, specifically validating comigration with contrast agents could be useful. Surrogate tracers might also not mirror the migratory capacity of targeted compounds since ligand binding might restrict uninhibited distribution within the interstitium. An added caution regarding surrogate tracers is their potential to affect therapeutic effectiveness or bioavailability. For the present study, the authors have not provided any relevant information to dispel such concerns. Precipitation, aggregation, and bioavailability assays would reinforce the notion that a surrogate tracer is not in any way affecting the therapeutic potential of a compound.

Understanding the relationship between the Vi and Vd is paramount to meaningful clinical trials using CED. Knowing this value for a particular tumor type and anatomical location provides some ability to predict a requisite Vd. In the present article, Lonser et al. reported a mean Vd/Vi ratio of 3.3 in 3 patients. Important to note is the wide range of variability in this ratio (1.6–4.1). Neverthe-
less, using that value, one can more accurately estimate the volume necessary to encompass a specific tumor or treatment volume. Generalizations regarding the volume of tumor burden (treatment volume) in DIPGs, however, are problematic owing to inconsistencies from one patient to another, lack of contrast enhancement of tumors, nebulus tumor margins, and profound changes in tumor volume throughout the disease course. It is not mentioned in the article, but based on the title of the clinical trial, most of these patients were treated at time of progression. Currently available measurements of mean DIPG volume range from 23 to 31 cm³ at the time of diagnosis to 16 cm³ after conventional treatment. There is no published information pertaining to mean tumor volume at the time of DIPG progression nor do the authors provide these data for their 4 patients. One can safely assume that this volume is at least equal to and probably greater than that at diagnosis. Using the currently reported Vd/Vi ratio of 3.3 and the published mean tumor volumes of 16–31 cm³, the requisite Vi for adequate tumor coverage would range from 4.9 to 9.4 ml. Given that the greatest Vi used in these patients was 3.7 ml, it is likely that greater volumes of infusion will be required with the continued evolution of this promising technique.

The authors have provided evidence that the concentration of Gd-DTPA as a surrogate tracer is important. This information will certainly be useful in the design of ongoing and future clinical applications that involve using CED in the brain, irrespective of the disease being treated. What remains unknown is the toxicity profile of differing concentrations of Gd-DTPA when administered directly into the brain. Surprisingly, no information is provided in this paper concerning patient safety. It remains unknown from the available data therefore whether 1 mM or 5 mM, or any concentration, of Gd-DTPA is safe for direct delivery. Approval for the use of Gd-DTPA will rely on such necessary information, and it is only hoped that this is included in future publications pertaining to this clinical trial.

In closing, this group deserves accolades for implementing a well—thought out and innovative clinical trial for children who otherwise have no legitimate therapeutic alternative. They are also pioneering the ability to dose—modulate on an individual basis using CED with a surrogate tracer, a profound step forward in the clinical acceptance of direct drug delivery to the brain. We can safely assume and expect further important clarification on this topic of drug delivery using CED from this group given their commitment and groundbreaking track record.

Disclosure

Dr. Souweidane reports being a consultant for Aesculap.

References


We appreciate Dr. Souweidane’s comments regarding our manuscript. In the study, we analyzed IL13-PE delivery using Gd-DTPA as a real—time surrogate MRI tracer in pediatric patients with DIPGs. We found that confusion of Gd-DTPA provided direct insight into convective delivery characteristics in this pathological condition. Specifically, it was possible to infer clinically relevant volumes of drug into the brainstem. The drug preferentially distributed along parallel white matter tracts, intraparenchymal air pockets, and previous cannula tracts. Finally, drug leak back along the infusion cannula could be detected in real time and was eliminated by reducing the rate of infusion. These findings should permit a greater insight into the properties of CED and enhance clinical application of this delivery technique.

Dr. Souweidane describes several factors important to surrogate imaging tracer use in CED. First, the accuracy with which the surrogate imaging tracer tracks drug distribution is critical. We and others have demonstrated, by using quantitative autoradiography in nonhuman primates and biomechanical modeling, that 5 mM Gd-DTPA most accurately tracks macromolecules in the size range of IL13-PE and over the infusion volumes described. While it is possible that physical property differences between tracer and drug could result in differing distribution volumes, we have not observed this with convective delivery of similar biologics when applying the bulk flow properties of CED. Second, surrogate imaging tracers could potentially affect bioavailability. We have previously shown that Gd-DTPA (5 mM) does not affect IL13-PE’s therapeutic effectiveness on glioma cells. Third, as Dr. Souweidane describes, DIPGs and other tumors are associated with heterogeneous imaging patterns, and determining treatment volume could be complex. To overcome this potential problem, it will be
important to develop trials (as the described trial does) that permit multiple infusions tailored to treat large volumes and unusual anatomical configurations. The use of Gd-DTPA allows on-the-fly adjustments of the infusion volume based on real-time distribution assessment, which will be important in tailoring treatments to individual patient needs. Finally, infusion of the surrogate tracer needs to be safe. In addition to the lack of toxicity described in the current patients, the safety of Gd-DTPA has been demonstrated in 1- and 5-mM concentrations in animals and in human patients. The ability to precisely identify drug distribution in real time should, in fact, enhance CED safety, as treatment can be directed and confirmed at only the desired anatomical site.

In conclusion, we very much appreciate Dr. Souwei-dane’s astute and considered comments regarding the use of surrogate imaging tracers in CED. His observations highlight the critical issues surrounding the development and use of surrogate imaging tracers in clinical convective drug delivery trials in the future. We agree that coinfusion of surrogate imaging tracers to track CED of therapeutic compounds in real time should permit better understanding of convective properties, allow for more effective delivery, provide direct insight into therapeutic efficacy, and permit the individualized treatment of a variety of neurological disorders. Furthermore, real-time MRI of CED provides a tool to modulate delivery characteristics to potentially improve patient outcome.

References


Please include this information when citing this paper: published online January 10, 2014; DOI: 10.3171/2013.10.PEDS13421.