Overcoming the Blood–Brain Barrier to Target Diffuse Intrinsic Pontine Glioma: What's New?

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INTRODUCTION

Diffuse intrinsic pontine glioma (DIPG), part of the broader diffuse midline glioma with H3 K27M mutation diagnosis, is a lethal brainstem tumor that most commonly occurs in children. Despite numerous clinical trials designed around radiation therapy and chemotherapy, to date none have made any significant progress in improving the outlook of this disease.[1] This begs the question, "Why?"

One of the primary barriers to delivering therapeutic drugs to the site of DIPG is access. The blood–brain barrier (BBB) serves as a natural protective sheath around much of the central nervous system, encapsulating the brainstem to inhibit the exposure to exogenous molecules and particles. Despite the known enhanced permeability and retention effect of most solid tumors, it is unclear how the BBB is affected in DIPG lesions.[2] Although radiation therapy has shown to be effective in prolonging survival of these patients by a matter of months,[3] there still remains a lack of effective therapeutics. In fact, no drug has ever shown benefit in a clinical trial; one of the major reasons being the ability to get drugs into the tumor.[1]

There is evidence to suggest that the blood brainstem barrier may be harder to deliver drugs through than the traditional BBB.[4] With that in mind, a new world of possibilities has materialized in which targeted and meaningful access to the brainstem may be achieved for treatment of DIPG tumors. Preliminary evidence suggests these techniques have the capabilities to overcome the BBB, and therefore could translate to effective drug therapies for this deadly disease.

CONVECTION-ENHANCED DELIVERY

Convection-enhanced delivery (CED) is neurosurgical approach involving stereotactic insertion of a catheter through the brain to directly deliver therapeutic agents to the region of interest. This approach involves the generation of a pressure gradient through slow infusion via intraparenchymal microcatheters to create fluid convection within the brain—increasing the penetration and distribution of the therapeutic agent.[5] Interstitial infusion by CED to the brainstem has been proven safe and feasible in multiple animal models, and recently a phase I clinical trial in children with DIPG validated this as safe in human patients.[6] In vivo studies from our laboratory have demonstrated that CED can achieve excellent biodistribution within the brainstem in regions that DIPG manifest, and that biodistribution is affected by the physical properties of the drugs, such as its inverse relationship with molecular weight (Figure 1).[7] Studies to optimize drug properties may further enhance the potential for CED to treat DIPG in the future.

PEPTIDE-GUIDED DELIVERY

The BBB is made of endothelial cells that overexpress a number of low-density lipoprotein receptors (LDLRs), including LRP-1, LRP-2, and LDLR.[8] The reason this is attractive for delivery mechanisms is that peptides, such as apolipoprotein E peptide, can induce transcytosis across the BBB due to its high affinity for these receptors. Therefore encapsulating novel therapies with apolipoprotein E peptides, delivery of the cargo across the BBB

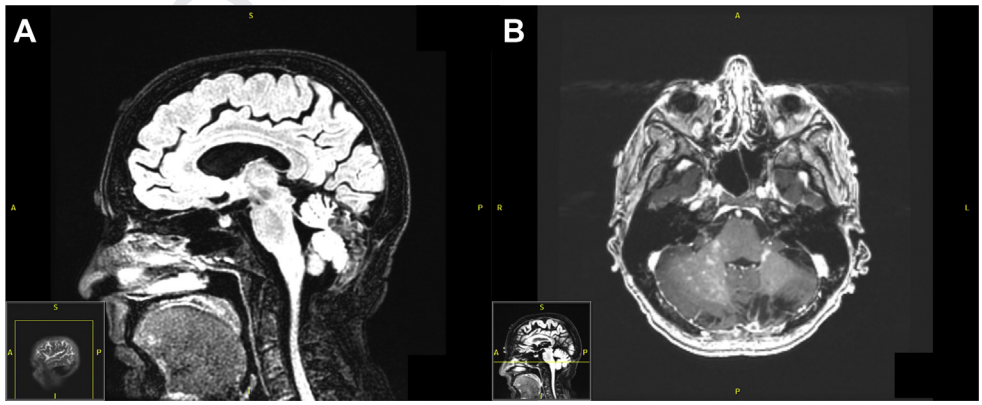

Figure 1. Using our established (**A**) patient-derived orthotopic diffuse intrinsic pontine glioma xenograft model, we evaluated the volume of distribution of (**B**) fluorescent infusate delivery via (**C**) a convection-enhanced delivery (CED) set-up to the brainstem of 6-week-old Sprague-Dawley rats (n = 3 per group) (**D**) over a number of infusate molecular weights 24 hours after infusion. CED was performed at a flow rate of 60 μL/hr for 1.5 hours. Data are presented as mean and standard deviation.

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could be enhanced. To date this has not been tested in the setting of DIPG but given its promising results in adult glioblastoma animal models,[9] it is of great interest to further investigate how peptide-guided delivery may distribute drugs throughout the brainstem.

FOCUSED ULTRASOUND DELIVERY

Another emerging drug delivery technique is the use of focused ultrasound (FUS) to disrupt the integrity of the BBB during therapy administration to improve cargo delivery, including traditional chemotherapeutic agents, as well as novel nanoparticle therapies. This technique uses low-frequency ultrasound waves in combination with intravenously administered microbubbles to transiently open the BBB without tissue injury by rearranging the endothelial tight junctions.[10] Attempts to utilize FUS to enhance drug delivery to the brainstem have already proven feasible in animal models.[4] Testing in tumor models and pediatric patients are required to understand how applicable FUS may be for DIPG patients, and clinical trials (NCT03028246) are now ongoing in pediatric patients.

CONCLUSIONS

The prognosis of patients with DIPG has always been dismal, despite constant and renewed attempts to utilize different chemotherapeutic and radiation approaches. There are multiple novel emerging drug delivery techniques to target DIPG lesions within brainstem that overcome the BBB, one of the primary barriers to targeting this disease. We hope and anticipate that neurosurgery will play a significant role in ascertaining the effectiveness of these techniques in human DIPG patients, as surgical specimens from patients will be the only way to determine real-time targeted biodistribution for these techniques. Surgical biopsy of these lesions in well-selected patients has already proven safe, and therefore we encourage its use in practice to allow us to ascertain how effective these novel delivery methods truly are.

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