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Chronic convection-enhanced delivery of MTX110 into the brainstem for pediatric diffuse midline glioma, phase I trial

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Abstract

Background: Diffuse Midline Gliomas (DMGs) are deadly and diffusely infiltrating gliomas. Histone deacetylase inhibitors have been found preclinically to be extremely active agents against DMGs but are limited by low blood-brain barrier penetration and systemic toxicity. Using an implantable subcutaneous pump in the abdomen connected to a catheter placed in the pons, we conducted a phase I, dose-escalation study to investigate the safety and feasibility of repeated infusions of MTX110, a water-soluble formulation of panobinostat, via convection-enhanced delivery (CED).

Methods: Eligible trial participants included pediatric patients 3-21 years old with newly diagnosed pontine DMG following radiation therapy. Patients underwent tumor biopsy followed by catheter and pump implantation, then received two 48-hour infusion pulses 7 days apart. Three dose levels of MTX110 infusions (30, 60, 90 mM) were studied. The infusion pump was prefilled with MTX110 and co-infused gadolinium, administered using the wireless N'Vision clinical programmer (0.2 mL/hr).

Results: Nine patients were treated in the study (30 mM, $n = 3$; 60 mM, $n = 4$; 90 mM, $n = 2$). All patients had an H3K27M mutated tumor. The treatment was well tolerated, and satisfactory tumor coverage was achieved in most patients. MRI vector analysis demonstrates reversible morphological changes in the brainstem during CED. One patient suffered a reversible, severe AE related to the infusion and tumor anatomy, and three patients had Grade 2 transient neurological deficits related to infusion ($n = 3$). Median PFS was 10 months from diagnosis (8-20 m) and median OS was 16.5 months (12-35m).

Conclusions: Chronic CED of MTX110 into the pons in DMG patients achieves satisfactory tumor coverage and is well tolerated. Further trials should evaluate chronic CED treatment with extended durations alongside non-invasive assessments.

Key points

- Chronic CED via subcutaneous pump is safe and feasible in pediatric DMG patients
- Repeated intrapontine infusions of MTX110 achieve satisfactory tumor coverage
- Novel MRI analysis shows reversible brainstem changes during chronic CED infusion

Importance of the study

Preclinical studies have identified several promising therapeutic agents, including histone deacetylase inhibitors such as panobinostat, which has demonstrated potent anti-tumor activity in DMG models. However, clinical translation has been hindered by the blood-brain barrier (BBB) limiting drug penetration, and systemic toxicity constraining dose escalation. Our study builds on prior evidence that CED can overcome these pharmacokinetic barriers by demonstrating the safety and feasibility of chronic CED using an implantable, refillable subcutaneous pump in pediatric DMG patients. We recently showed that this approach is effective in adult glioblastoma patients, and here we extend its application to pediatric patients with DMG, achieving high drug distribution and tumor coverage in the pons with a high tolerance rate. Importantly, we introduce novel non-invasive imaging methodologies to assess the reversibility of dynamic brainstem changes during drug infusion and addressing a critical gap in real-time monitoring of local drug delivery. These findings establish a new paradigm for chronic, localized drug delivery in pediatric neuro-oncology and by eliminating the need for repeat surgeries and allowing sustained drug administration, this approach opens avenues for prolonged treatment regimens, including multi-drug combinations and novel therapeutic classes.

Introduction

Diffuse midline glioma (DMG), previously known as diffuse intrinsic pontine glioma (DIPG), is the most common malignant brainstem glioma in children and remains one of the deadliest pediatric cancers with a median survival of only 9 to 12 months.[1-3] Although radiation therapy remains the primary standard of care, it provides only transient benefits.[2] Importantly, DMG is characterized by its diffusely infiltrative growth pattern, where malignant cells extend beyond the boundaries detectable on standard imaging.[4] This extensive spread underscores the necessity of targeting tumor cells not only in the T2 hyperintense regions but also in the peritumoral brain tissue, where infiltrative tumor cells reside. Novel therapeutic strategies are urgently needed that can effectively target invasive tumor cells without causing harm to surrounding brain tissue.

Molecular studies of DMG, including transcriptional and metabolomic screens, have identified multiple avenues for drug targets as well as several chemotherapeutic and targeted therapy agents with favorable preclinical therapeutic results.[5-7] Panobinostat is one of these identified drugs with strong preclinical efficacy in DMG models. Panobinostat has been shown to restore H3K27 trimethylation—a critical factor in the epigenetic dysregulation seen in DMG—while reducing tumor proliferation and increasing tumor cell death.[7,8] However, like many potentially effective agents, panobinostat has limited ability to cross the blood-brain barrier (BBB), in part because it is a substrate for BBB p-gp and BCRP efflux pumps.[9] As a result, systemic administration of panobinostat has been largely ineffective clinically.[10] A phase I trial of oral panobinostat was conducted in pediatric DMG without any observed clinical benefit, likely because the maximum tolerated dose was limited by increasingly severe myelosuppression.[10]

Convection-enhanced delivery (CED) has emerged as a promising technique for local drug delivery to overcome blood-brain barrier (BBB) limitations and toxicity associated with systemic delivery.[11,12] With CED, drugs are distributed directly into the interstitial space of the brain by bulk flow, achieving higher drug concentrations while minimizing systemic toxicities.[12-14] The feasibility and safety of CED for delivering chemotherapeutics in brain tumors, including DMG has been previously demonstrated.[15-19] However, challenges remain, particularly regarding the achievement of multiple infusions, consistency of drug distribution and the predictability of coverage. Historically, CED relied on external pumps which limited treatment to a single infusion of limited duration to minimize infection risk. However, single, short-duration CED infusions are insufficient to sustain the drug concentrations necessary for clinical efficacy, especially for anti-proliferative agents that target tumor cells throughout the cell cycle.[20,21] Previously, repeated infusions have required an additional surgery for catheter placement, leading to decreased quality of life and increased infection risks.[22]

To address these limitations, we engineered a unique implantable CED pump and catheter system capable of delivering sustained, repeatable infusions without the need for additional surgeries. This strategy allows for non-invasive refills and long-term drug administration, offering a new avenue for chronic CED treatments in DMG patients.[23] The goals of this clinical trial were to evaluate the safety and feasibility of using chronic implantable CED pumps in pediatric DMG patients for the first time to improve drug delivery

effectiveness. In addition to analyzing standard clinical and radiographic outcomes, we employed advanced MRI methodologies that adjust for morphological dynamics in the brainstem, enabling precise, high-resolution assessments of drug distribution and monitoring of structural alterations within the pons.

Methods

Study design and patient selection

This study was an IRB approved (CUMC IRB #AAAS2936), investigator-initiated, single-center, prospective phase 1 clinical trial conducted at NewYork- Presbyterian-Columbia University Irving Medical Center (New York, NY, USA). Patients were recruited from the Pediatric Oncology and Pediatric Neurosurgery practices/clinics at Columbia University Irving Medical Center and were all seen by an attending physician (SZ) who is an investigator on the trial. Prior to study enrollment, appropriate written informed consent (and assent, as applicable), was obtained from all patients and parents/guardians. The study was terminated after the 9th patient completed the study due to multiple competing trials and staffing support issues during the COVID-19 pandemic which led to the withdrawal support from the sponsor company. Three escalating concentrations of MTX110 (30, 60, 90 μM) were originally planned in this study. This precluded the enrollment of a final patient at the highest planned drug concentration (four patients were enrolled at the 60 μM concentration, see below).

MTX110 is an aqueous formulation of panobinostat, an HDAC inhibitor known to inhibit HDACs at nanomolar concentrations. The terminal half-life of panobinostat is approximately 37 hours when delivered systemically, although a half-life of 13 hours has been reported in pediatric patients.[10,24] Panobinostat has a logP of 2.643, and maximum solubility of approximately 200 uM at pH 7.6 with increasing solubility at lower pH's.[9] While BBB penetrance of panobinostat has been reported in murine models, panobinostat is a substrate for p-gp and BCRP efflux pumps in primates, limiting its brain penetrance.[9,25]

Eligibility

Eligible patients were aged 3 to 21 years old with newly diagnosed diffuse midline glioma. Prior therapy was restricted to field radiotherapy (54Gy) and CSF diversion for hydrocephalus. All patients had a radiological diagnosis of pontine DMG confined to the region of the pons and occupying at least 50% of the pons. While a confirmed H3K27 mutation was not necessary for eligibility, all enrolled patients were eventually confirmed to have H3K27M mutations. Additional eligibility criteria included a Karnofsky performance status or Lansky play score of ≥70 and the absence of radiological evidence of cystic changes or hematoma in the pons obstructing the planned CED catheter trajectories. Patients with evidence of metastatic CNS disease on standard of care MRI scans were excluded. Standard laboratory tests were required before enrolment, including but not limited to serum chemistry, complete blood count, coagulation studies, and pregnancy tests (if applicable).

Treatment procedures

CED planning and procedure

Treatment included two, 48-hour pulses of MTX110 through a surgically placed intracerebral catheter connected to a subcutaneously implanted, refillable pump, and subsequent removal of the pump and catheter. A pre-treatment MRI was performed prior to catheter placement to optimize catheter trajectory selection and optimal CED and tumor coverage. If a biopsy had not been collected prior to enrollment, the stereotactic biopsies of the tumor were acquired through small twist drill holes for additional immunohistopathological analyses. For patients undergoing biopsy for histopathologic evaluation, catheter placement proceeded with a cranial incision and burr hole through a single catheter into the tumor. CED was delivered using a commercially available, 1.5 mm diameter silastic Spetzler lumbar shunt catheter (Integra, Plainsboro, NJ) as previously described by our team.[23] The catheter was connected to a refillable SynchroMed II infusion pump (Medtronic; Minneapolis, MN, USA) implanted in the abdomen through silastic tubing that was subcutaneously tunneled. The catheter was placed in the geometric center of the tumor at a site chosen to maximize coverage of the tumor and adjacent infiltrated brain tissue based on spherical distribution. The entire drug delivery system is depicted in **Figure 1A and B**.

Infusion protocol

The infusate, prepared by the hospital research pharmacy, included a combination of 1:100 gadolinium Gadavist (GE Healthcare; Marlborough, MA, USA) plus MTX110 (30, 60, or 90 uM) (Hycamtin; GlaxoSmithKline; Research Triangle Park, NC, USA). The final concentration of gadolinium in the infusate is 0.01 M. Active infusion began on post-operative days 1-3 at the discretion of the attending neurosurgeon to allow time for expected and routine recovery from surgery. Treatment included two, 48-hour pulses of therapy interspersed by 5-7-day rest periods. During each pulse, patients received MTX110 at 0.2 mL/hr for 20 hours, followed by a 4-hour rest period with a reduced flow rate of 0.048 mL/hr to maintain catheter patency. This cycle was then repeated (daily volume = 4.2 mL; total volume = 8.4 mL). Pumps were percutaneously refilled in patients before each pulse of therapy using a designated Medtronic SynchroMed II refill kit at the bedside. During infusion cycles, the patient's vital signs were regularly examined, and neurological functions were assessed when awake. The five to seven days between pulses consisted of a rest period during which the pumps were set at the minimum programmable rate of saline (2 uL/hr; 5-7-day volume = 0.24-0.34 mL). Once infusions were initiated, they were carried out over a total of approximately 10 days. After the second pulse of therapy on week 2, patients were taken to the OR for pump and catheter removal. A full timeline is depicted in **Figure 1C**.

Image-guided CED schedule

Serial MRIs were performed throughout the treatment period for quality checks of proper catheter placement, drug delivery, and possible treatment response of the tumor. Before initiating each pulse of therapy, a T2-weighted MRI was done to confirm adequate catheter placement.

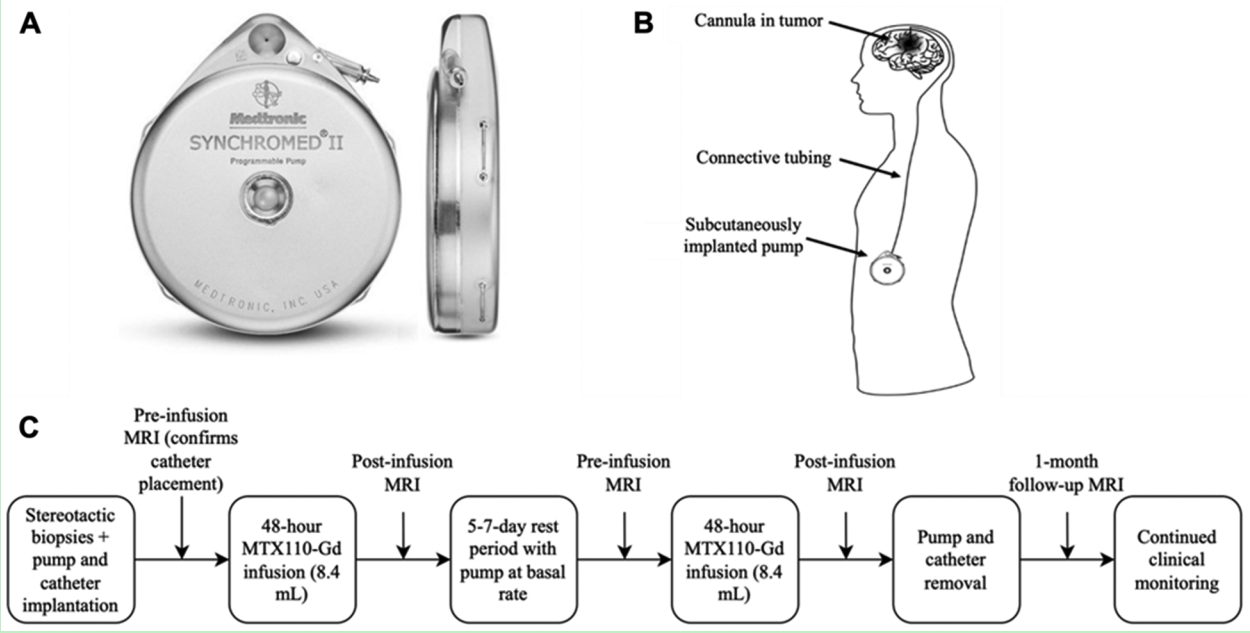

Figure 1 CED system and treatment schema. (A) Programmable CED pump, implanted subcutaneously, with a refillable reservoir. (B) Schematic of complete CED system, with pump, connective tubing, and catheter implanted in the tumor. (C) Timeline of implantation, CED infusions, MRIs, and removal of pump and catheter.

Gadolinium was co-infused during each pulse of therapy, and a T1-weighted MRI was used to estimate drug distribution and identify possible backflow, as done in previous studies.[22,26] If necessary, pediatric patients were sedated for their MRI by a pediatric anesthesiologist.

Treatment response parameters

Primary and secondary outcomes

The primary endpoint of the current study was to evaluate the feasibility, safety, and Maximum Tolerated Dose (MTD) of chronic MTX110 CED in children with diffuse midline gliomas. Outcomes were defined as adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0).

Secondary endpoints included determining the objective response rate of MTX110 via chronic CED in this population, progression-free survival (PFS) and overall survival (OS) times from diagnosis, steady state volumes of drug distribution, and quality of life in both the patient and parents/guardians of the patient being treated.

Radiological assessments

Tumor response and progression were evaluated using the international criteria proposed by the updated Pediatric Response Assessment in Neuro-oncology (RANO) guidelines,[27] which use radiographic measures to determine tumor progression. The volume of drug distribution was estimated by visualization of co-infused gadolinium on T1-weighted MRI. To standardize voxel intensities across subjects, we applied a histogram-matching algorithm[28] using the cortex of a reference subject for normalization of T1-weighted images. Voxels from the target and template were converted to intensity histograms, then to cumulative distributions, and the correlation between distributions was maximized such that:

$$\max_{a,b}\left(a \cdot f(x)+b, g(x)\right)$$

where $f(x)$ is the target distribution, $g(x)$ is the template distribution, and a and b are the parameter estimates. After normalization, the pre-infusion T1-weighted image was subtracted from the post-infusion T1-weighted image to create a difference image, which was then thresholded.

The threshold corresponding to the maximum signal-to-noise ratio was determined by computing max(S-N), where S = the probability density function of voxel intensities in the pons (signal) and N = the probability density function of voxel intensities in the cortex (noise). Voxels exceeding this threshold and contiguous with the largest cluster were binarized to generate a mask representing the gadolinium distribution volume. Tumor masks were generated using a semi-automated approach in which the T2-weighted MRI was thresholded such that only the tumor was visible and then multiplied by a pons mask to eliminate any false positives outside the pons. The percent of tumor or pons treated was computed by intersecting the mask of the tumor or pons and the mask of gadolinium distribution:

$$\%\ \text{target treated} = \frac{\text{volume}(\text{targetmask} \cap \text{gadoliniummask})}{\text{volume}(\text{targetmask})}$$

Brainstem morphologic analysis

Previous studies are limited by the ability to accurately measure true pre- and post-gadolinium changes during local

drug infusions due to morphological changes in parenchyma during treatment. To evaluate brainstem morphological changes during and after CED, the current study utilized a novel method of brain imaging registration that can account for morphological changes before and after treatment. Each patient's T1-weighted MRIs were nonlinearly registered to their respective pre-infusion MRIs using FSL's Nonlinear Image Registration Tool (FNIRT).[29] This process generated a nonlinear warp field for each patient, detailing voxel-wise motion across imaging sessions and allowing visualization of motion vectors throughout the brain.

In each patient's pre-infusion T1-weighted MRI, pons masks were manually contoured, while fourth ventricle masks were created semi-automatically, as previously described. Warp fields were applied to these pre-infusion masks, creating updated masks in subsequent sessions that reflect morphological changes due to CED infusion and during the rest period and follow-up period. This procedure was performed for the tumor, pons, and fourth ventricle masks. Volumes of the pons and fourth ventricle were measured for each session, and the bicaudate index was calculated using T1-weighted MRI images to check for hydrocephalus.

QoL and neuro-cognitive functioning

Quality of life and neuro-cognitive functioning were examined in patients undergoing CED treatment as well as their parents and/or guardians, where applicable. The validated Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health 7+2 measures were utilized, which assess an individual's physical, mental, and social health.[30] PROMIS scales were administered pre-treatment and at various post-treatment times through in-person assessments or virtually through Qualtrics or email communication. PROMIS scales are a T-score with a mean of 50 and a standard deviation of 10. Higher scores represent more of the measured concept (eg, a score of 60 in global physical health is one standard deviation better (healthier) than the general population). PROMIS scores have been shown to correlate with symptom burden as rated by both pediatric brain cancer patients and parents.[31]

Dose escalation and potential adverse events

Dose escalation followed an accelerated titration design (ATD) format using 30, 60, or 90 uM concentrations of MTX110 at a consistent volumetric flow rate of 200 uL/hr. Concentration increased with dose escalation during Phase 1 of the study. At the first dose-limiting toxicity (DLT) occurrence, the ATD was transitioned to a standard 3+3 dose escalation design. That is, two additional subjects were to be accrued at the dose level that triggered the transition. Compatibility data suggested that about 10% of the drug is retained in the Medtronic SynchroMed II pump, and therefore dose adjustments were based on these results accordingly. The Data Safety Monitoring Committee was consulted before a decision on dose escalation for any patient.

DLTs were defined as any new (or increased from baseline), treatment-related (drug and/or device) neurological deficits as found on neurological examination, which is grade 3 or higher or symptomatic intracranial hemorrhage or stroke of any grade. These deficits include, but are not limited to, changes in level of consciousness, new onset speech difficulties (aphasia, mutism, dysarthria), confusion, visual field deficits, focal weakness, and/or seizures. The DLT period is defined as 14 days (at least) after the second infusion. Furthermore, DLT criteria included any systemic treatment-related Grade 3 or higher hematologic or non-hematologic toxicity within 14 days after the infusion.

Statistical analysis

Demographic and clinical variables were summarized by mean or median for continuous variables and by frequency and rate for categorical measures. The rates of adverse events and dose-limiting toxicity were calculated along with

Table 1 Baseline clinical and pathological data. Additional information on histopathological analysis is included in the supplementary material table S3. All patients underwent RT in the month following their initial diagnosis. None of the patients had a CSF diversion procedure or hydrocephalus prior to CED catheter placement. Follow-up data on re-irradiation following study treatment was not collected

Patient #	Age (years)	Sex	Diagnosis and histopathology/sequencing	Diagnosis to treatment (months)
1	6	F	H3K27M (IHC), TP53 positive, Ki67: 25.1%, EGFR negative, PTEN retained	4
2	4	F	H3K27M (IHC), TP53 negative, Ki67: 2%, EGFR negative, PTEN retained	7
3	10	F	H3K27M (IHC), TP53 positive, me3H3 negative, Ki67: 10.12%, EGFR negative, PDGFRa positive, PTEN retained	4
4	5	M	H3K27M (IHC), TP53 positive, me3H3 positive, PTEN retained, ACVR1 p.G328V: -47%, CDKN2C p.T22fs: 28%	3
5	5	M	H3K27M (IHC), Ki67: 1.8%, TP53 negative, EGFR negative, PDGFRa negative, PTEN retained	6
6	17	F	H3K27M (IHC), TP53 positive, Ki67: 2.5%, PDGFRa negative, BRAF V600E negative	5
7	9	M	H3K27M (IHC, whole exome sequencing), PIK3CA-mutant by whole exome sequencing, Ki67: 1.4%	7
8	5	F	H3K27M (IHC), Ki67: 1.8%, TP53 negative, PDGFRa negative, BRAF V600E negative, PTEN negative	5
9	4	F	H3K27M (IHC), BRAF V600E negative, Ki67: 2%	5

Table 2 Grade 3 or higher treatment related adverse events

	N, events	*N* (%), patients
Total events	6	9
Investigations		
Lymphocyte count decreased	1	1 (11.1)
Nervous system disorders		
Facial Palsy/Facial Muscle Weakness	1	1 (11.1)
Glossopharyngeal nerve disorder	1	1 (11.1)
Recurrent laryngeal nerve palsy	1	1 (11.1)
Gastrointestinal disorders		
Dysphagia	1	1 (11.1)
Other		
Surgical and medical procedures – other, specify	1	1 (11.1)

All patients received systemic dexamethasone to decrease inflammation and edema. Steroid-induced effects of lymphocytopenia ($n = 2$) and generalized muscle weakness ($n = 1$) were rare AEs.
Three patients experienced COVID-19 during treatment, 1 of which died during treatment.

a 95% confidence interval. Kaplan-Meier analyses were used to assess PFS and OS from the time of initial diagnosis. All statistical analyses were performed in R studio (http://www.rstudio.com/) and Matlab (http://www.mathworks.com/).

Result

Patient characteristics and tumor pathology

A total of 9 patients were enrolled between March 1, 2019, and April 1, 2021. Basic demographic and clinical data of enrolled patients are described in **Table 1**. Patients were 67% ($n = 6$) female and 33% ($n = 3$) male. They were of the median (IQR) age of 5 (4-17) years. All patients (100%) had biopsy-proven H3K27M DMG tumors. The median (range) time from diagnosis to treatment was 5 (3-7) months.

Prior to treatment enrollment, 8 (89%) had H3K27 mutations defined on immunohistochemical or molecular analyses (**Table 1**), although one patient was treated prior to knowing their H3K27M status. Since biopsies were obtained at the time of catheter placement, H3K27 mutations were eventually confirmed in all 9 (100%) of patients. Tumors generally had low Ki67 labeling index (median, 2% [1.4-25.1]), except for patients 1 and 3, which had 25.1% and 10%, respectively (**Supplementary Material Table S2**). Additional immunohistochemical markers are presented in **supplementary material table S3**.

Clinical and radiological treatment response outcome

Safety and toxicities

A total of twenty-six potential procedure and/or treatment-related or non-related adverse events occurred in our study (**Supplementary Table 1**). All AEs were transient and resolved within 1 month of treatment in each patient. Of these, 8 (31%) were most likely or probably related to the surgical procedure itself. These deficits were limited to focal neurological deficits in one patient and minimal pain at the surgical site in two patients. There were no catheter-related infections, surgical site bleeding, or new or worsened signs of increased intracranial pressure.

One patient had a grade 4 glossopharyngeal and laryngeal nerve palsy related to the infusion. Radiographic imaging during treatment noted an asymmetrical tumor with infusate pooling on one side of the brainstem causing focal cranial nerve deficits due to brainstem compression. However, the infusion was immediately stopped upon noting these clinical changes and the patient returned to baseline approximately two weeks later. The patient only received one 48-hour infusion and stopped treatment after this event causing another patient to be recruited into the 60uM cohort.

One (11%) patient's catheter was misplaced during initial catheter placement and was revised on post-operative day 1. The patient continued treatment with good subsequent results regarding CED delivery of MTX110.

There were no AEs specifically related to MTX110 and no dose-limiting systemic toxicities related to the drug. Maximum tolerated dose was not achieved given the early closure of the trial given that panobinostat was no longer commercially available.

Chronic CED infusion feasibility

The imaging analysis included six patients with two pulses and one patient with one pulse. Patient #3 did not receive the second dose due to leaving the trial early. Patient #1 was not included in the imaging analysis due to a pump failure that was noticed because co-infused gadolinium was not observed on the follow up MRI scan. Patient #4 was not included in this analysis because of a misplaced catheter. Assessment of gadolinium distribution during CED allowed for estimation of drug distribution[23] throughout the pons before, during, and after both infusions (**Figure 2A**). The first infusion achieved extensive coverage of the T2-hyperintense tumor (mean: 80%; range: 58%-97%) and of the entire pons (mean: 67%, range: 42%-84%). For the second infusion, there was a decrease in coverage of T2-hyperintense tumor (mean: 68%, range: 45-96%; $P = .03$) and pons (mean: 55%, range: 39%-82%; $P = .04$) relative to the first infusion (**Figure 2B and C**). The gadolinium distribution volume was high for both infusions, with a mean of 22 cm^3 (range: 15-29 cm^3) for the first and 20 cm^3 (range: 14-25 cm^3) for the second (**Figure 2D**), with no significant difference between the two infusions ($P = .12$). An illustration of gadolinium distribution throughout the visible tumor and pons for the first infusion is shown in **Figure 2E**; a similar distribution was seen for the second infusion.

CED dynamics in the pons

Nonlinear registration of the brainstem across sessions shows that CED infusion causes a radial expansion and posterior translation of the pons towards the fourth ventricle and cerebellum, which is reversed during the 2-month follow-up period. Two examples are shown in **Figure 3A**, with outlines of the pons at each time point highlighted, demonstrating a return to baseline at follow-up. **Figure 3B** shows representative displacement vectors and magnitude for the pontine expansion during CED infusion.

As a result of the infusion, the pons volume increased by a mean (SD) of 17% (6%) across the first infusion and 12%

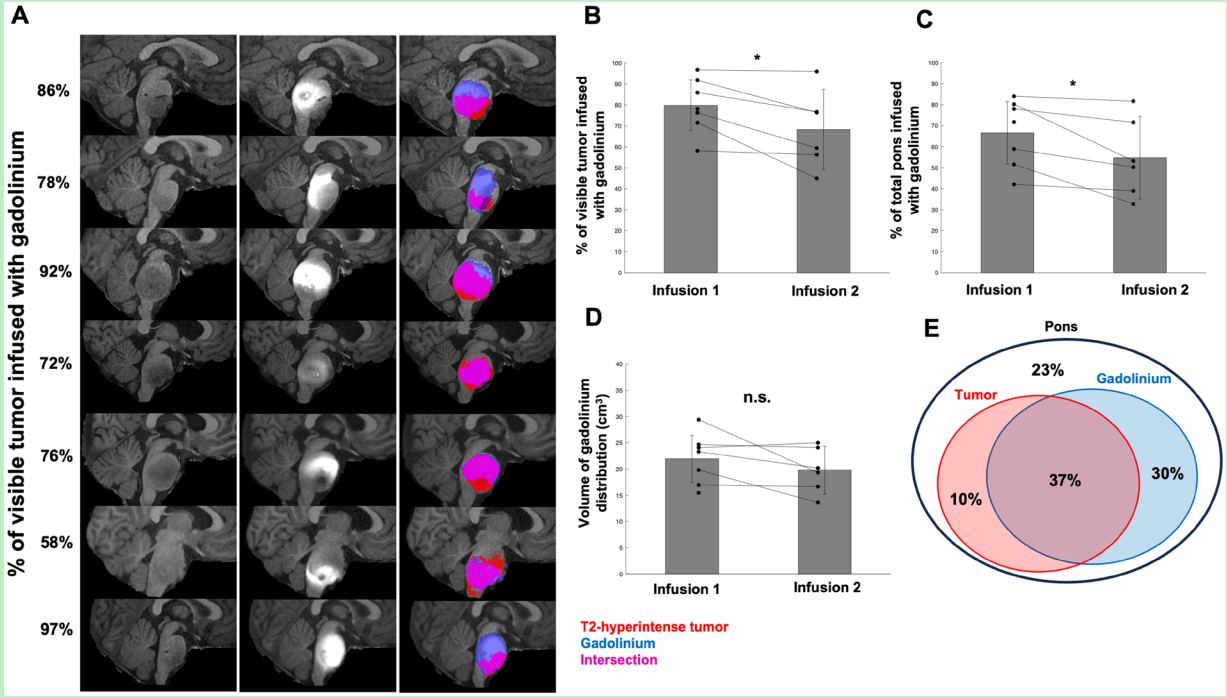

Figure 2 Radiological coverage of the tumor and pons by CED of MTX-Gadolinium. (A) Images of all 7 patients before (left column) and after (middle column) the first infusion and regions identified as visible tumor (based on T2-hyperintensity), gadolinium, and intersection (right column). For each infusion, the percent of visible tumor covered with gadolinium (B), percent of the total pons covered with gadolinium (C), and volume of gadolinium distribution (D) is shown. (E) A Venn diagram demonstrating the average spatial relationship between visible tumor, gadolinium distribution, and the entire pons for the first infusion. *$P < .05$.

(5%) across the second without clinically observable symptom change in all patients. There was a reduction in pons volume by 6% (5%) during the rest period, however, the volume remained 10% above baseline ($P < .001$). Importantly, by the ~2-month follow-up session, pons volumes had all returned to baseline in all but one patient (due to tumor recurrence) (Figure 3C). The fourth ventricle volume was also assessed to estimate CED dynamics in the pons and for possible radiological, subclinical evidence of hydrocephalus. The fourth ventricle had a mean (SD) decrease in volume of 13% (6%) after the first infusion, returned to baseline during the rest period ($P = .51$), and then decreased by 11% (9%) after the second infusion before returning to baseline at follow-up (Figure 3D). The median (range) bicaudate index after the first infusion was 0.077 (0.058-0.105) and 0.095 (.066-0.109) after the second. At follow-up, the median bicaudate index decreased to 0.083 (0.066-0.117), which were within normal limits for the patient's age.[32] Importantly, no patients were found to have clinical signs of hydrocephalus at any point. None of the patients had a history of CSF diversion or hydrocephalus at the beginning of the study.

Clinical outcomes

Median survival from time of diagnosis was 17 (12-35) months and progression-free survival was 10 (8-20) months. The median time of follow-up from the pump explant was 20 (12-26) months (Table 3). All patients had completed the study protocol as described and there was no obvious correlation between treatment dose and survival in this small cohort. There was no correlation between the location of disease progression and the gadolinium distribution.

All patients ultimately demonstrated progression during long-term follow-up. All patients developed recurrence within the treatment field. One patient had distant metastases.

Quality of life assessments in patients and parents

Quality of Life (QoL) assessments were limited in the current study. Two patients along with their parents had long-term follow-ups beyond 3 months (patients 2 and 5). QoL via standardized PROMIS assessments in these patients demonstrate relatively stable QoL assessments up to 6-9 months. Patient 2 had PROMIS scores of 34 (0-3 months), 25 (4-6 months), and 24 (6-9 months). While their parents ranged from 30 (0-3 months), 22 (4-6 months), and 28 (6-9 months). Patient 5 had a baseline score of 31 and a 4-6 month follow-up score of 27, while their parents had a baseline score of 22 and a 4-6 month follow-up score of 22. QoL scores below the general population mean of 50 are expected for pediatric DMG patients, with progressive worsening as the disease progresses.

Discussion

CED is a local-regional drug delivery method to directly infuse therapeutic agents into tumor and peritumoral tissue by bulk flow, driven by a pressure gradient. This technique bypasses the BBB to achieve a high concentration of drug throughout the tumor bed without systemic toxicities that are typically

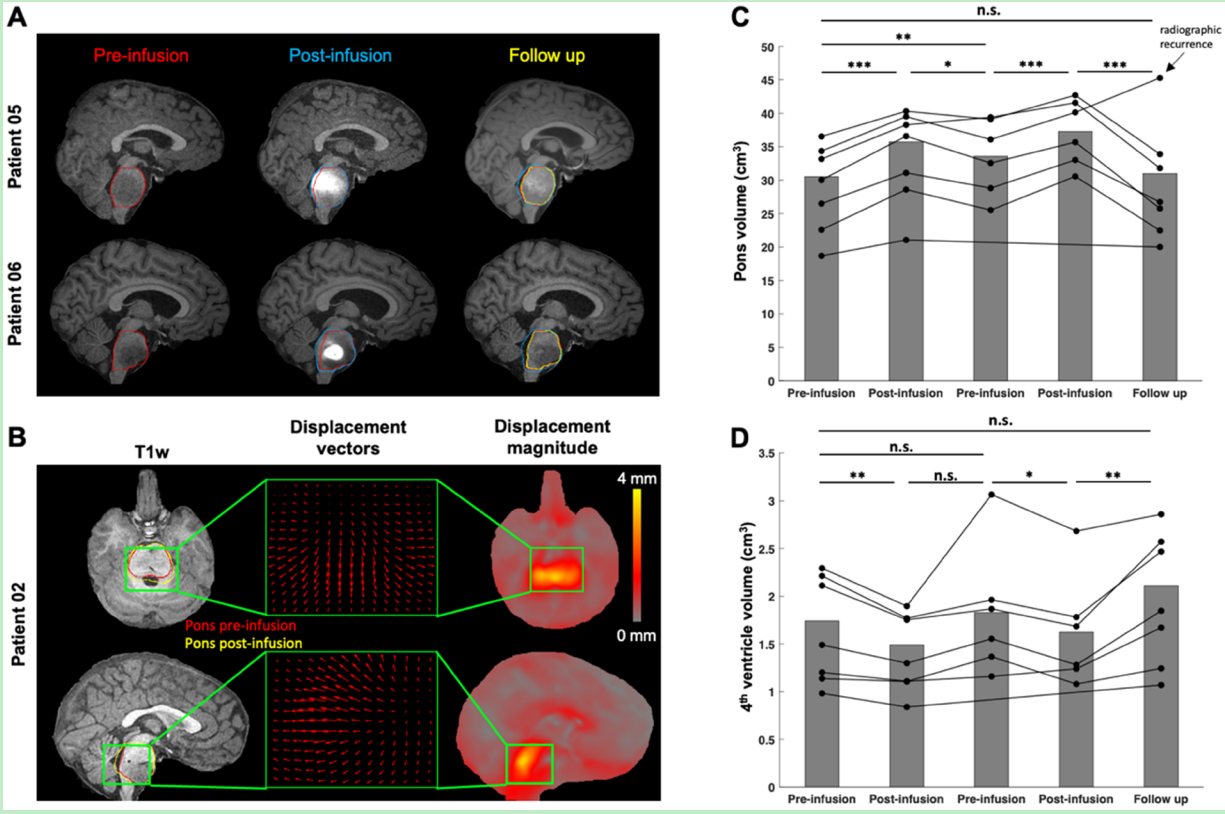

Figure 3 Reversible morphological changes from CED infusions demonstrate brainstem elasticity. (A) Two examples of pre- and post-infusion morphological changes and return to baseline. Pons outlines are shown for the pre-infusion (red), post-infusion (light blue), and follow-up (yellow) scans. (B) Displacement vectors describing voxel-wise movement and displacement magnitude maps as a result of CED infusions. Changes in pons volume (C) and fourth ventricle volume (D) across time points. *$P < .05$, **$P < .01$, ***$P < .001$.

Table 3 Treatment response clinical characteristics

Patient #	MTX-110 dose (μM)	PFS from diagnosis (months)	PFS from CED (months)	OS from diagnosis (months)	OS from CED (months)	Time to follow up (months)
1	30	10	5	14	10	14
2	30	20	13	26	19	26
3	30	12	8	17	13	17
4	60	10	8	16	13	16
5	60	8	2	12	6	12
6	60	17	12	N/A	N/A	34
7	60	12	5	24	17	24
8	90	10	5	N/A	N/A	24
9	90	9	4	15	10	15

associated with conventional systemic chemotherapy.[12-14] The ability to bypass the BBB is important for DMG, which has shown a preclinical vulnerability to panobinostat, a drug that poorly penetrates the BBB in primates.[9] Previous studies have shown the CED is a feasible drug delivery technique for pediatric pontine gliomas, but these studies have been limited to a single infusion per surgery.[33,34] Whether the use of multiple catheters (as described by Szychot et al.[5]) can provide superior coverage by the infusate without causing more toxicity than using a single catheter remains to be proven. Our clinical trial is the first formal trial to utilize CED with a novel subcutaneously implanted pump in DMG patients, providing the advantage of repeated, sustained infusions without the need for additional surgeries. We examined the feasibility of this strategy in children with DMG, and through advanced imaging analyses, we assessed CED dynamics in the pons, demonstrating significant infusion volumes with predictable patterns of tissue expansion and recovery.

Previously, CED for DMG treatments relied on single-use external pumps that required a separate surgical procedure for repeated infusions, each requiring surgical intervention.[22,36-38] To address this limitation, we successfully demonstrated the feasibility and safety of using a subcutaneously implanted, refillable pump. Chronic drug delivery with repeat infusions provides a sustained therapeutic exposure within the tumor over time, as shown in our clinical trial for adult glioblastoma (GBM) patients.[23] Importantly, a single CED infusion may be insufficient to achieve adequate tumor coverage and maintain therapeutic drug concentrations within the parenchyma for a sufficiently long amount of time. Our study achieved a mean tumor coverage of approximately 69%, significantly higher than the 24.7% mean coverage per infusion or the 56% cumulative coverage across multiple infusions from multiple surgeries reported in a recent trial at UCSF.[22] This enhanced coverage underscores the efficacy of chronic CED enabled by an implantable pump system, which ensures more consistent and extensive drug distribution across the tumor bed while minimizing surgical risks.

A key outcome of our study was the demonstration of safety in a highly vulnerable pediatric cohort. Overall, approximately one-third of the patients experienced transient grade 2 neurological deficits, with no permanent symptoms observed. One patient experienced transient neurological deterioration due to asymmetric infusion-related brainstem compression, which was promptly recognized, allowing the infusion to be stopped and ultimately resulting in the patient returning back to baseline. Importantly, there were no dose-limiting toxicities (DLTs) or systemic toxicities, and the maximum tolerated dose (MTD) was not reached by study closure. These findings are consistent with prior studies that have shown transient adverse effects related to CED but highlight the safety advantage of using an implantable pump to reduce surgical risks and systemic exposure.[22] Median survival from time of diagnosis was 16.5 (12-35) months and progression-free survival was 10 (8-20) months, though the small sample size in this feasibility study limits any conclusions about the treatment's efficacy. Single-infusion CED has also been associated with worse QoL compared with baseline,[22] which is attributed to the need for multiple surgeries. Because only two patients completed QoL assessments at the 6-month follow-up time point, formal analysis of QoL and cognitive outcomes was not conducted. Such assessments should be made in future chronic CED trials of DMG, as was done in adult GBM.[23]

Another significant challenge in CED is the high variability in the volume and direction of drug distribution as previously observed.[21,22] This variability is thought to be related to the anisotropy of brain tissue, which causes differences in permeability based on the tissue's directional properties.[39,40] White matter often allows drugs to spread preferentially along its tracts, resulting in uneven distribution across the tumor bed. Additionally, factors such as drug-specific responses to anisotropy and tissue permeability further complicate drug delivery, with some agents penetrating more effectively in anisotropic tissues, while others distribute more uniformly in isotropic regions.[39,40] The relative differences in permeability of gadolinium and panobinostat through anisotropic tissue are unknown. Preclinical work will have to correlate the relative concentrations of each in the infusion zone, as taking multiple biopsies of the pons is not clinically feasible in pediatric DMG patients.

In our cohort, we achieved high coverage of the pons with gadolinium, which we know to include both T2-hyperintense lesions as well as diffusely infiltrating disease not visible on standard-of-care imaging. Interestingly, subsequent infusions at the same rate resulted in decreased coverage of the T2-hyperintense lesion, which could be due to various reasons such as increased water content in an expanded pons, changes in tissue compliance, residual drug, or backflow. Importantly, extending the duration of drug exposure with chronic CED is crucial to targeting tumor cells that cycle asynchronously through different stages of division. By maintaining a prolonged drug presence, the likelihood of exposing a greater number of proliferating cells to the therapeutic agent at optimal times is maximized. Gadolinium-based contrast agents are commonly co-infused to track drug distribution during CED via MRI. However, this approach is known to underestimate the volume of drug distribution as effective drug concentrations have been measured beyond the MRI-visualized gadolinium in our previous chronic CED study. Our prior study of CED in recurrent glioblastoma demonstrated that topotecan distribution extends beyond radiographic contrast enhancement, and the authors expect MTX110 to behave similarly, although future work will have to correlate gadolinium and MTX110 distributions. Drug-tagging techniques such as SPECT and PET may be utilized to assess drug distribution directly.[41]

Our study utilized advanced MRI vector analysis to overcome the registration challenges in inter-MRI comparisons caused by the CED infusions, so that we can more accurately monitor dynamic changes in the brainstem. We observed that the pons expanded concentrically toward the cerebellum, causing some compression of the fourth ventricle. Notably, although the pons gradually returned to baseline two months after the final infusion, it did not fully return to baseline between individual infusions. However, the fourth ventricle volume did return to baseline during the rest period, and no patients ever developed clinical hydrocephalus, indicating we maintained a safety margin of infusion parameters and monitoring that future studies may use as a basis.

We demonstrate that the brainstem undergoes reversible morphological changes, indicating an ability to accommodate multiple CED infusions with clinically acceptable safety. This analysis provides valuable insights for future studies, as it provides information to optimize infusion protocol parameters. Adjustments may be made to pulse length, infusion intervals, and rates. If we can determine the drug's effective half-life within the pons, this information taken together can help to achieve an ideal balance between drug coverage and concentration. This approach also opens the possibility of tailoring infusion protocols to each patient's specific anatomical and physiological characteristics, ultimately enhancing treatment outcomes with greater consistency and control.

In conclusion, this study demonstrates the feasibility and safety of a novel, chronic CED approach for DMG treatment, using a subcutaneously implanted pump that enables repeated, sustained drug infusions directly into the brainstem with precise, real-time drug monitoring—overcoming blood-brain barrier limitations and reducing the need for

multiple surgeries. While early termination precluded the determination of the MTD (primary study endpoint), we found concentrations up to 90 μM to be safely tolerated. Chronic CED achieved substantial tumor coverage and was generally well tolerated by patients. Future studies should focus on improving the effectiveness of chronic CED by optimizing treatment variables such as the optimal number of infusions, infusion flow rates, use of other drugs and/or drug combinations, as well as refining imaging and biomarker assessments to ensure accurate, real-time monitoring of drug distribution. Ongoing innovation and research in these areas are essential to advancing treatment options and improving outcomes for children facing this devastating disease.

Supplementary material

Supplementary material is available at *Neuro-Oncology Pediatrics* online.

Keywords

CED, DMG, DIPG, Brainstem, MTX110, Chronic

Lay summary

In this pediatric patient cohort with pontine DMG, we demonstrate the ability to deliver a therapeutic agent through chronic CED with a subcutaneous implantable and refillable pump. Chronic CED allowed for repeated infusions of MTX110 without repeat surgery. Major surgical-related adverse effects were limited, and chronic treatment with a subcutaneously implanted pump was well tolerated by all patients with no instances of hydrocephalus. This is the first trial in pediatric patients demonstrating the ability to infuse a therapeutic agent multiple times using a subcutaneous pump to avoid the need for repeat surgery. This novel treatment approach addresses the current limitations associated with drug delivery in DMG patients and provides a template for prolonged treatment with other promising candidate therapeutic agents.

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Conflict of interest statement

JNB has a consulting agreement with Theracle, Inc. Other authors declare no conflicts of interest.

Author contributions

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Data availability

All data included in the current manuscript is deidentified and could be made available in part or whole per reasonable request to the authors.

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