Poster # 1442: High Dose MTX110 (Soluble Panobinostat) Safely Administered into the Fourth Ventricle in a Non-human Primate Model

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Introduction

New strategies are needed to treat medulloblastoma and other malignant tumors that originate in the posterior fossa in children. Systemic chemotherapy causes considerable toxicity and is often ineffective in a recurrent setting. Local delivery of chemotherapeutic agents directly into the fourth ventricle is a novel treatment approach that may play a role in treating children with these tumors. Prior studies in our laboratory in piglets and non-human primates have demonstrated that various chemotherapeutic agents can be safely infused into the fourth ventricle without causing new neurological deficits or evidence of damage to the brain on MRI scans or histological analysis. The objective of the current study is to evaluate safety and pharmacokinetics of MTX110 (soluble panobinostat) infusion into the fourth ventricle of the brain. Panobinostat is a histone deacetylase inhibitor (HDACi) that is chosen for further study based upon prior work demonstrating that HDACi’s are promising candidates for decreasing medulloblastoma tumor growth in orthotopic, patient-derived models. This study tested the safety and pharmacokinetics of short-term and long-term administration of MTX110 (soluble panobinostat; Midatech Pharma, UK) into the fourth ventricle of non-human primates.
Methods

Four rhesus macaque monkeys underwent posterior fossa craniectomy and catheter insertion into the fourth ventricle. In Group I (n=2), catheters were externalized and lumbar drain catheters were placed simultaneously to assess cerebrospinal fluid (CSF) distribution after short-term infusions. MTX110 (0.5 ml of 300 μM panobinostat solution) was infused into the fourth ventricle daily for five consecutive days. Serial CSF and serum panobinostat levels were measured. In Group II (n=2), fourth ventricle catheters were connected to a subcutaneously-placed port for subsequent long-term infusions. Four cycles of MTX110, each consisting of 5 daily infusions (0.5 ml of 300 μM panobinostat solution), were administered over 8 weeks. Animals underwent detailed neurological evaluations, MRI scans, and post-mortem histological analysis.
Results

Figure 1: MRI scans obtained after MTX110 infusions

Figure 1a: Sagittal T2-weighted MRI in primate 1. The arrow points to the catheter within the fourth ventricle. Figure 1b: Axial T2-weighted MRI in primate 1. The arrow points to the catheter within the fourth ventricle. Figure 1c: Sagittal FLAIR MRI in primate 3. No abnormal signal changes are noted in the brainstem, cerebellum, or elsewhere after infusions.

Figure 2: H&E stained section showing cerebellum, fourth ventricle and pons from primate 1. Insert demonstrates a higher magnification image of the region within the blue circle in the tegmentum, showing focal disruption of the ependymal lining (black arrow) and focal perivascular inflammation (white arrow).
Figure 3: Mean panobinostat levels in CSF sampled from the fourth ventricle and the lumbar cistern over the first 12 hours post-infusion into the fourth ventricle in Group I animals. Panobinostat levels 24 hours post-infusion were undetectable in either location. Data points represent the mean for n=2 (0.25, 1, 2, 4, and 8 hours) or n=1 (12 hours) for fourth ventricle samples and n=2 (0.25, 1, and 4 hours) or n=1 (2 hours) for lumbar cistern samples. Error bars represent standard deviation.

Figure 4: Mean CSF panobinostat levels at peaks and troughs over 4 cycles of daily infusion into the fourth ventricle in Group II animals. Data points represent the mean for n=4 in Cycle 1 and n=2 in all other cycles. Error bars represent standard deviation.
Overall: No neurological deficits occurred after intraventricular MTX110 infusions. MRI scans showed catheter placement within the fourth ventricle in all 4 animals, with extension to the cerebral aqueduct in one animal and into the third ventricle in one animal. There were no MRI signal changes in the brainstem, cerebellum or elsewhere in the brain in any animals. Histologically, the cytoarchitecture of the brain was preserved with only focal mild post-surgical changes in all animals. Serum panobinostat levels at two and four hours after infusion were undetectable in all samples in both groups. In Group I, the mean peak panobinostat level in fourth ventricle CSF (6242 ng/ml) exceeded that in lumbar CSF (9 ng/ml) by greater than 600-fold. This difference was statistically significant (p < 0.0001, paired t-test). In Group II, mean peak CSF panobinostat level (11,042 ng/ml) was significantly higher than mean trough CSF level (33 ng/ml; p<0.0001).
Discussion

This study describes the first reported intraventricular or intrathecal administration of MTX110, a soluble form of panobinostat, in an animal model. Panobinostat is a chemotherapeutic agent that may be promising for the treatment of medulloblastoma. This study demonstrated that MTX110 can be safely infused into the fourth ventricle of the brain in non-human primates. Of note, the study was performed in rhesus monkeys that did not harbor brain tumors. There is no adequate large animal model of medulloblastoma, and these experiments would be technically challenging, if not impossible, in small animal models.

An advantage of direct infusion of panobinostat into the fourth ventricle over systemic infusions is the high drug levels that can be achieved with fourth ventricle infusions. In the current experiments, peak measurements in fourth ventricle CSF obtained 15 minutes after infusions were extremely high (mean of 6242 ng/ml for primates in Group I and mean of 11,042 ng/ml for primates in Group II). By comparison, in a recent review article describing pharmacokinetics of panobinostat, pooled data of multi-dose studies showed a maximum plasma concentration of 21.6 ng/ml one hour after 20 mg of oral panobinostat. Despite the extremely high CSF panobinostat concentrations in the primates in our study, none showed any neurological impairment or evidence of damage to the brain on imaging studies or histological analysis. Thus, direct infusion of MTX110 into the fourth ventricle is worthy of further investigation to determine if this approach may benefit patients with medulloblastoma or other malignant tumors originating or recurring in the fourth ventricle.
Summary Points

- MTX110 (soluble panobinostat) can be safely infused in the fourth ventricle in non-human primates at high supra-therapeutic doses.
- Post-infusion CSF panobinostat levels peak immediately in the fourth ventricle and then rapidly decrease over 24 hours.
- Panobinostat is detectable at low levels in CSF measured from the lumbar cistern up to 4 hours after infusions.
- These results will provide background data for a pilot clinical trial in patients with recurrent medulloblastoma.