High dose MTX110 (soluble panobinostat) safely administered into the fourth ventricle in a non-human primate model

DDEL-09

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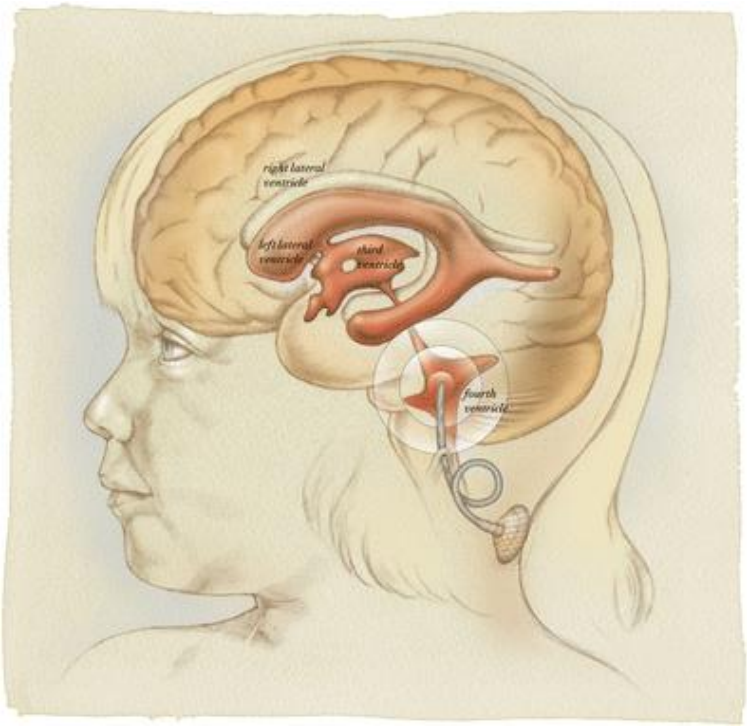
Drug delivery in pediatric neuro-oncology

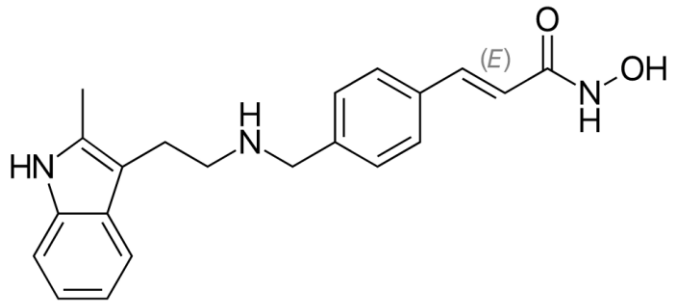
- The blood-brain barrier (BBB) remains a significant obstacle to effective treatment of pediatric brain tumors, particularly in a recurrent or metastatic setting
- Direct administration of chemotherapy to the CSF is one method that could bypass the BBB to improve tumor exposure to drug while minimizing systemic toxicity

- Instillation of a 4th ventricle catheter enables loco-regional delivery of chemotherapy
  - Preclinical (Sandberg, et al., J Neurosurg Pediatr 2008; Sandberg, et al., J Neurooncol. 2010; Sandberg, et al., Sandberg and Kerr, Childs Nerv Sys 2016; Sandberg, et al., J Neurosurg Pediatr 2020)
  - Clinical (NCT02458339, NCT02905110, NCT02940483)

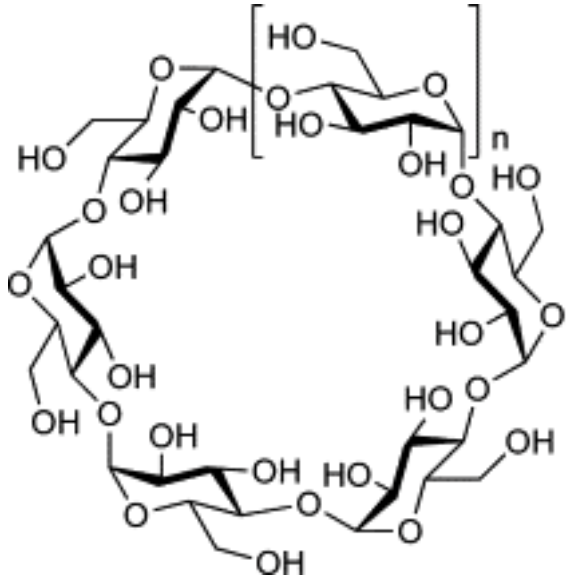


Sandberg and Kerr, Childs Nerv Sys 2016

Panobinostat (LBH-589)



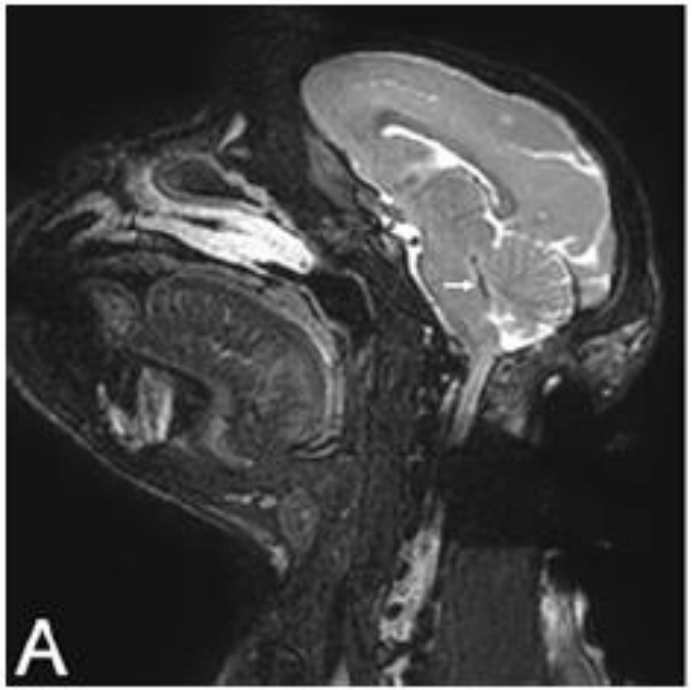
- Histone deactylase inhibitors (HDACi)
  - Histone acetylation is frequently disregulated in cancer
  - HDACi promote acetylation of histones, which yields anticancer effects
- Panobinostat (LBH-589)
  - Pan-HDACi demonstrated to be efficacious against multiple pediatric brain tumors, including Group 3 medulloblastoma (MB)
    - Pei, et al., Cancer Cell 2016
  - Very poorly water soluble and lipophilic (logP ~2.8)
- MTX-110
  - Water soluble formulation of panobinostat achieved via a cyclodextrin inclusion complex (produced by MidaTech Pharma)

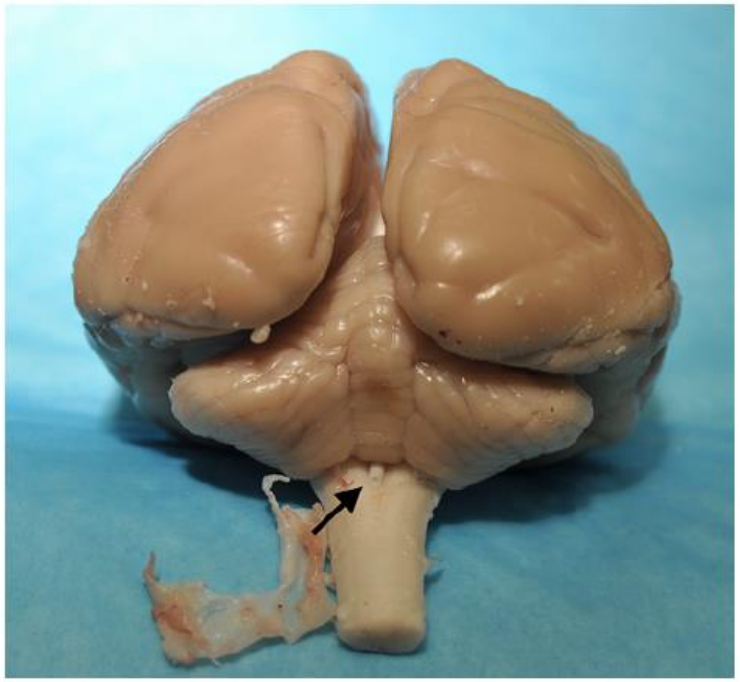


Approach

- Instillation of 4th ventricle catheter
  - 4 rhesus macaque monkeys
  - Posterior fossa craniectomy
  - Insertion of 4th ventricle catheter and lumbar drain
- Drug infusion and sampling
  - Infusions consist of 0.5mL of 300uM panobinostat (as MTX110)
  - **Group I (n=2)**: 1 treatment cycle consisting of 5 daily, consecutive infusions
  - **Group II (n=2)**: 4 treatment cycles performed over 8 weeks
  - Sampling of plasma, 4th ventricle CSF, and lumbar CSF conducted at regular intervals
- Analyses
  - Detailed neurological evaluations
  - MRI scan to confirm catheter placement
  - Postmortem histological assessment of brain, spinal cord, and peripheral tissues
  - Plasma and CSF processed by mass spectrometry for pharmacokinetic measurements

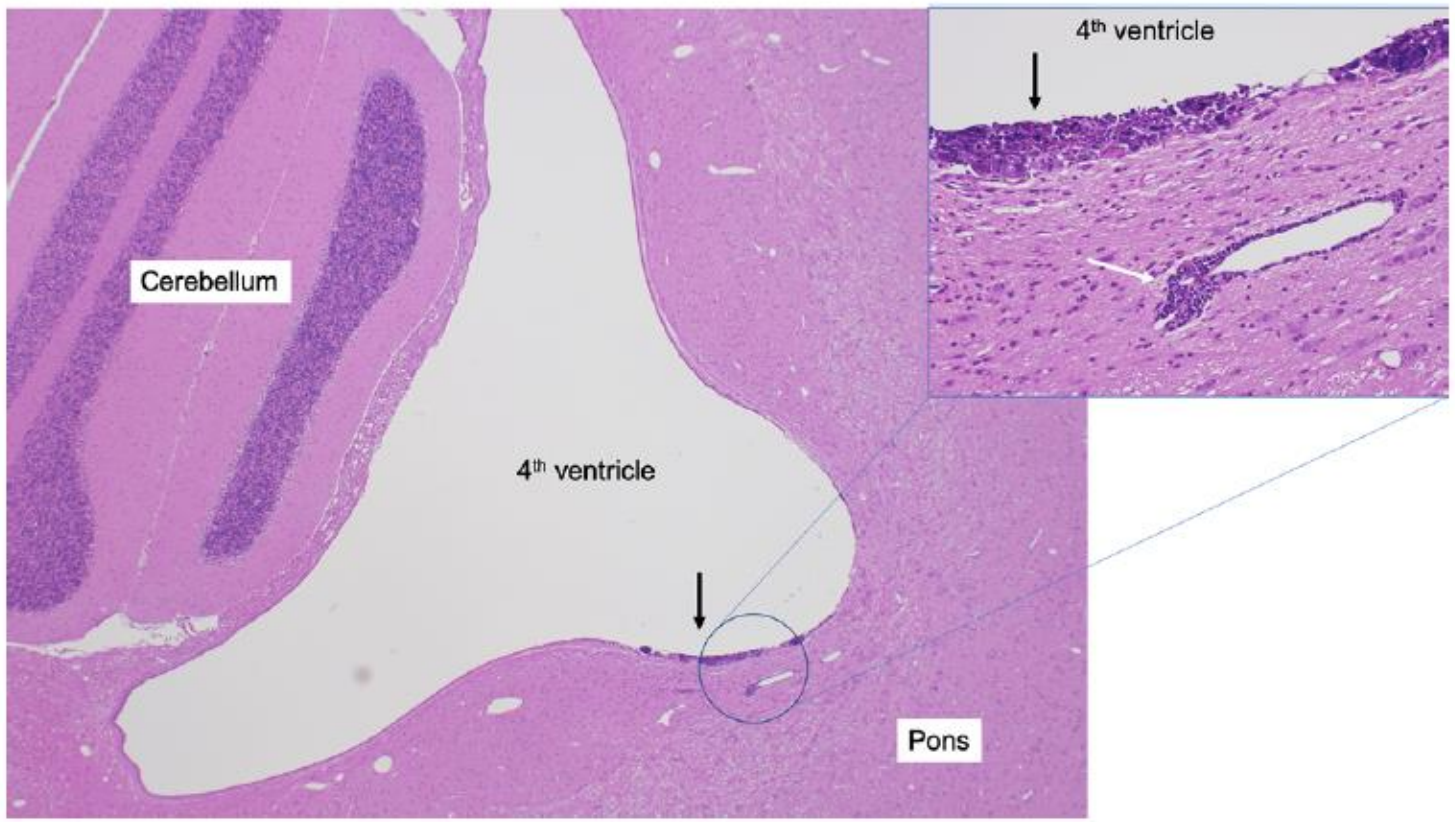
Results: catheter placement





- Catheter placement was confirmed by MRI and visual inspection at necropsy
- Ventricles were of normal size with no evidence for any gross abnormality

Results: toxicity

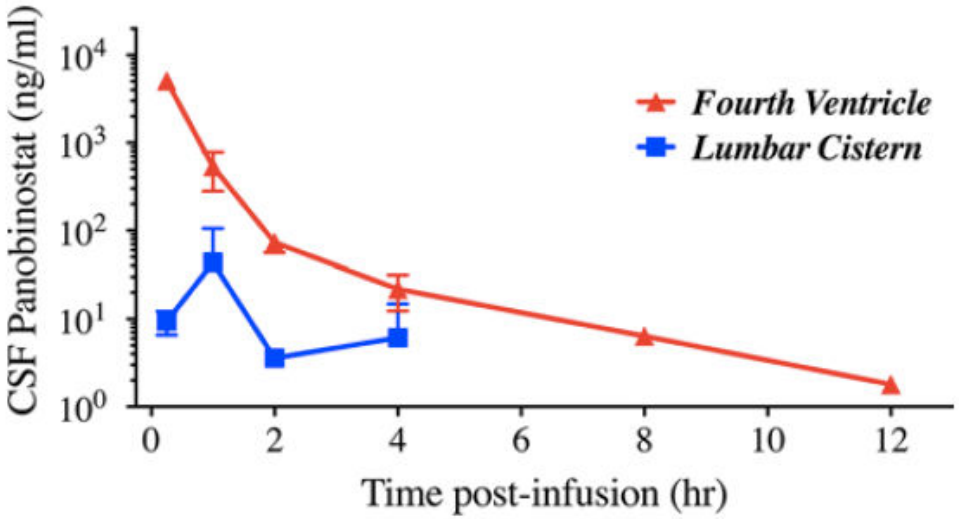


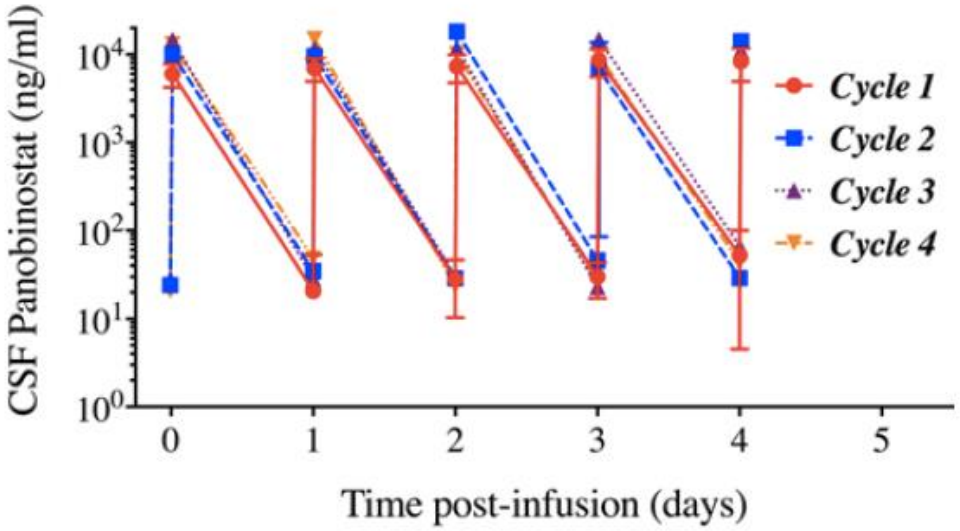
- Detailed neurological / behavioral assessments were normal throughout the study
- Focal ependymal disruption in the pons was observed in 3 out of 4 primates, which was most likely a result of catheter placement. Mild, focal inflammatory infiltrates were observed regionally in the meninges, choroid plexus, and subependymal zone of the brainstem
- All other assessments were normal

Sandberg, et al., J Neurosurg Ped 2020

Results: drug levels

- No panobinostat was detected in any plasma sample
- Drug levels were highest in the 4th ventricle samples and declined over time
- Lumbar samples yielded lower concentration of drug that became undetectable at later time points
- Repeat dosing studies demonstrated highly reproducible peak/trough levels with no evidence for drug accumulation over multiple treatment cycles





Conclusions

- 4th ventricle catheters were successfully instilled in rhesus macaque monkeys to enable locoregional infusion of the chemotherapeutic agent MTX110 (water soluble panobinostat)
- Treatments were well-tolerated, with no evidence of toxicity under this dosing regimen
- Drug levels in the 4th ventricle and lumbar samples suggest rapid distribution of panobinostat and likely clearance to tissue and/or via turnover of CSF
- Drug levels in the CNS reached a therapeutic range
- These preclinical data support an expectation of safety for administration of MTX110 via the 4th ventricle
  - Clinical trial is ongoing (NCT04315064)

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