Diffuse Pontine Gliomas
(Progress and Future Potential)

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Disclosures

- None
Fast Facts for DIPG

• Without radiation survival approximately 4 months

• Survival is 30% at one year and less than 10% at 2 years.

• Long term survival 2-3 % usually associated with atypical imaging and clinical features

• Multiple studies investigating medical therapy
Diagnosis of DIPG

- Initially describe in 1985
- Symptoms duration less than 6 months
- Symptoms related to brainstem dysfunction
- Pons involvement greater than 2/3 (50-66%)
- Bright signal on T2 and hypointense on T1
DIPG: How are we doing?

Most children die within two years

Fig. 3 Whole overall survival of the DIPG biopsy children (a) and according to the WHO grading (b)

23 year old white male that presented with left hemiparesis
• Multiple chemotherapy regimens
• Radiation
• Symptoms resolve, presents to us to discuss next steps.
• Stereotatic Needle biopsy
Neurosurgeon’s Previous Role: Surgery is not the answer!

Old thoughts!
Stereotactic Biopsy of Pontine lesions

• Two routes: transcortical and transcerebellar.

• Transcortical
  • Can sample lesions at all brainstem levels
  • Stereotactic navigation is necessary

• Transcerebellar
  • Fewer eloquent structures at risk
  • Preferred for upper medullary and pontine masses
Complications (series of 130 DIPG patients)

- Morbidity of 3.9%; all deficits temporary
- Worsening of preexisting ataxia
- Ataxia and VI and VII nerve palsy
- Isolated VI nerve palsy
- 4 patients had small clinically insignificant hemorrhage
- Morbidity rates 0-25% with most transient in other series
On side of lesion
Ataxia of limbs and gait (more prominent in bilateral involvement): Pontine nuclei

On side opposite lesion
Paralysis of face, arm, and leg: Corticobulbar and corticospinal tract
Variable impaired touch and proprioception when lesion extends posteriorly: Medial lemniscus
Diffusion Tensor Imaging (DTI) fiber tracking AP view (hand)
Periodically verify accuracy by navigating on known anatomical landmarks.
Biopsy Trajectory
Internuclear Ophthalmoplegia

1. Absence of adduction of the eye on the affected side.
2. Convergence is preserved.
3. Nystagmus of the unaffected eye on lateral gaze.
Brainstem syndromes

(A) Diagram showing brainstem structures and eye movement directions:
- Lateral rectus
- CN VI
- Oculomotor (CN III) nucleus
- Medial longitudinal fasciculus (MLF)
- Abducens (CN VI) nucleus
- Paramedian pontine reticular formation (PPRF)

(B) Lesions and their effects on gaze:

<table>
<thead>
<tr>
<th>Lesion 1</th>
<th>Right abducens nerve (CN VI palsy)</th>
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<tr>
<td>Lesion 2</td>
<td>Right abducens nucleus (right lateral gaze palsy)</td>
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<tr>
<td>Lesion 3</td>
<td>Right PPRF (right lateral gaze palsy)</td>
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<tr>
<td>Lesion 4</td>
<td>Left MLF (left INO) Nystagmus</td>
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<td>Lesion 5</td>
<td>Left MLF and left abducens nucleus (1½ syndrome) Nystagmus</td>
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Conclusions

• Transcerebellar is preferred route for biopsy of DIPGs
• Most complications are temporary and involve eye movements
• Deeper biopsies can affect motor pathways
• New approaches are needed to make progress in treatment of DIPGs because current therapies are failing
Surgical Biopsy for Diffuse Intrinsic Pontine Glioma

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Disclosure

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DIPG - 1996

Natural History
“Diffuse tumors have terrible prognosis with most patients dead in 12 months.”

Treatment
“The most common neoplasm is the diffuse variety. These are malignant. Can be diagnosed on basis of MRI (pontine). Biopsy felt unnecessary. Radiation offered as palliation.”

“MR scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: A report from the children's cancer group” (Albright et al, 1993)
DIPG BATS - Rationale

MGMT promoter methylation correlates with improved PFS and OS
Hegi, et al. MGMT and temozolomide in GBM (NEJM 2005)

EGFR expression in DIPG
Gilbertson (2003): 4/7 demonstrated EGFR +

Pediatric Phase I and II experience
RT+TMZ (II); erlotinib+TMZ (I); XRT+bevacizumab+TMZ (I/II)

Little molecular data is available to guide development of new agents

New strategies are needed; current molecular assays require small amounts of tissue available through stereotactic-guided biopsies
Surgical Biopsy


N = 24; histologic diagnosis made in all (they have now done over 100 cases)
Dx: Malig astrocytoma (22), low grade astro (1), PA (1)
No periop deaths; 2 transient CN deficits (<2 mos), 1 worsening of pre-morbid hemiparesis


N = 10, high diagnostic yield
1 post-op diplopia; 1 altered therapy
DIPG-BATS Summary

Biopsy

MGMT methylation - EGFR expression

1. MGMT + EGFR -
   - radiation
effective
   - temozolomide
   - erlotinib
   - bevacizumab

2. MGMT + EGFR +
   - radiation
effective
   - temozolomide
   - bevacizumab

3. MGMT - EGFR +
   - radiation
effective
   - erlotinib
   - bevacizumab

4. MGMT - EGFR -
   - radiation
   - bevacizumab
Objectives

Phase II

primary objective is to estimate PFS/OS of children with DIPG treated with a molecularly-based treatment strategy, as compared to historical controls; patient survival will be correlated with tissue markers of EGFR expression and angiogenesis

evaluate the safety and feasibility of a surgical biopsy of non-disseminated, diffuse, intrinsic pontine gliomas

assess toxicity of the four treatment strata

molecular analysis of specimens acquired during biopsy
Planned Biologic Studies

MGMT methylation
EGFR/ EGFRvIII
  IHC for expression, FISH for gene amplification

Additional IHC
  VEGF, p-AKT, PDGFR, PTEN

Gene expression array, SNP array

Whole genome sequencing
  Whole exome sequencing
  OncoMap: mutational analyses of kinome, tumor suppressor genes, oncogenes and other regulators of cell proliferation
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<th>Participating Institutions</th>
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<tr>
<td>UCSF</td>
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<tr>
<td>Dana Farber Cancer Institute</td>
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<td>Lurie Children’s Hospital (Chicago)</td>
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<td>Children’s Hospital Los Angeles</td>
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<td>Seattle Children’s Hospital</td>
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<td>Kosair Children’s Hospital (Louisville)</td>
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<td>Penn State Hershey Medical Center</td>
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<td>Cook Children’s Medical Center</td>
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<td>Stanford University</td>
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Surgical Biopsy

Target selection - *optional adjuncts*
- areas of post-gadolinium contrast enhancement, or
- abnormal regions determined by 2D MR spectroscopy, or
- areas of increased metabolism determined by PET scan, or
- areas of increased MR perfusion, or
- tumor distinct from major white matter pathways as determined by DTI

‘Ideal’ tumor features
- homogeneous tissue features on MR
- necrotic or cystic areas are minor features (do not select largely necrotic areas)
- adjacent to cerebellar peduncle
Entry point generally over midpoint of cerebellar hemisphere, at least 1 cm below transverse sinus

Single burr hole with coagulation of dura and cerebellar surface

Standard closure, with burr hole closure (plate, cement, or none) according to surgeon preference
Neuronavigation system positioned to allow direct entry and visualization as biopsy needle is advanced

‘Free-hand’ technique avoided
Tissue Samples

6.2.4 Tissue Handling. 4 specimens should be obtained. An initial tissue specimen will be used for histologic confirmation of tumor. A second tissue specimen will be used for immunohistochemical evaluation of tumor. Additional specimens (specimens number three and four) will be obtained for molecular analysis (see section 9). These specimens can also be used for immunohistochemical verification if insufficient material is obtained in sample 2.

Tissue handling, storage and shipping, whether performed directly or delegated, is the primary responsibility of the study neurosurgeon.

Sample 1 stays at biopsy site, samples 2-4 are sent to Neuropath Core Lab.
Results – Adverse Events

Total of >50 patients enrolled

1 patient with somnolence, possibly related to biopsy
1 patient with grade 2 ICH, possibly related to biopsy
1 patient with epidural hematoma, related to biopsy
PNOC - Participating Institutions

UCSF Benioff Children’s Hospital San Francisco & Oakland

Children’s Hospital Los Angeles
University of Washington - Seattle Children’s Hospital
Oregon Health Sciences University
Children’s Hospital of Philadelphia
University of California Los Angeles – Mattel Children’s Hospital
University of Utah – Primary Children’s Hospital
University of California San Diego – Rady Children’s Hospital
Children’s National Medical Center
St. Jude’s Children’s Research Hospital
Children With Newly Diagnosed DIPG

- Candidate for Biopsy/Resection
  - No: Patient cannot be enrolled
  - Yes: Patient is eligible
    - Biopsy/Clinical Pathology
      - Yes: Adequate sample: > 50% tumor
        - Yes: Gene Expression Profiling, WES & Predictive Modeling (TGEN) → Report
          - Specialized Tumor Board issues treatment recommendation
            - Patient will be monitored for safety and clinical response
          - Evidence of Progression/Recurrence: patient can be re-consented for repeat biopsy
        - No: Off study
      - No: Off study

Correlative Studies:
- Xenograft development
- Circulating Tumor DNA
- WGS
Primary Objective

Feasibility: To determine the feasibility of a specialized tumor board making individualized treatment recommendations within 21 business days of tumor tissue collection, using RNA based expression analysis, WES and predictive modeling for children and young adults with newly diagnosed DIPGs.
PNOC 003 - Objectives

Secondary Objectives

To determine the safety and describe the toxicity of using a molecularly based treatment approach and specialized tumor board recommendation in children and young adults with newly diagnosed DIPG.

To determine the safety and describe the toxicity of using a molecularly based treatment approach and specialized tumor board recommendation in children and young adults with progressive/recurrent DIPG.

To evaluate the safety of performing biopsy and obtaining tissue for molecular and genomic profiling in children and young adults with newly diagnosed DIPG.

To evaluate the safety of performing biopsy and obtaining tissue for molecular and genomic profiling in children and young adults with progressive/recurrent DIPG.
**PNOC 003 - Feasibility**

**Primary Objective:** To determine the feasibility of a specialized tumor board making individualized treatment recommendations within 21 business days of tumor tissue collection, using RNA based expression analysis, WES and predictive modeling for children and young adults with newly diagnosed DIPGs.

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<thead>
<tr>
<th>Total Enrolled</th>
<th>17</th>
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<tr>
<td>Eligible Patients</td>
<td>15</td>
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<tr>
<td>Patients Completed</td>
<td>14</td>
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<tr>
<td>Feasibility Failures</td>
<td>1</td>
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<tr>
<td>Ineligible Patients</td>
<td>2</td>
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Business days from surgery to tumor board call (average): **18.5 days**

Business days from surgery to treatment recommendation (average): **20.3 days**
Results – Adverse Events

Some patients with transient neurologic deficits
One patient with a delayed intra-tumoral hemorrhage
Convection-Enhanced Delivery (CED)

An approach for delivery of small and large molecules to targeted sites in solid tissues, utilizes bulk flow to deliver and distribute macromolecules to clinically significant volumes of tissue.  


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

Toxicity evaluation of prolonged convection-enhanced delivery of small-molecule kinase inhibitors in naïve rat brainstem

Sharon L. Ho · Ranjodh Singh · Zhiping Zhou · Ehud Lavi · Mark M. Souweidane
PNOC 009

CED with liposomal irinotecan
Co-infusion with gadolinium
Repeated infusion with the goal of covering the total tumor target
Dissemination
Cerebellum
Summary

Upfront therapy in conjunction with detailed genetic and epigenetic characterization

Multimodality therapy including CED, intra-arterial delivery
  • implantable systems
  • real-time visualization

Multiple targets to be treated simultaneously