Treatment Opportunities in Diffuse Intrinsic Pontine Glioma (DIPG)

Mark Kieran, MD, PhD

FDA pedsODAC Meeting
June 29th, 2016
Disclaimer

I was the PI of the first US biopsy and targeted therapy clinical trial of newly diagnosed DIPG patients

This presentation may contain copyrighted images and material and is intended solely for use in a live classroom education setting. Further distribution or reproduction is prohibited
Disclosures and Support

• I have no stocks, patent rights or employment with any company

• I have/had consulting/advisory board agreements with Novartis  Boehringer  Lilly
  Sanofi  Incyte  SigmaTau
  Merck  Bayer

• I have pre-clinical laboratory and/or clinical trial support from the following companies:
  Advantagene  Merck GA  Amersham
  Novartis  AstraZeneca  Transmolecular
  Celgene  Wyeth
Brainstem Tumors

• 10% of pediatric brain tumors
  – 80% DIPG
    • 100% malignant
  – 20% not primarily of the pons
    • 80% low-grade, 20% malignant

• Median age 6-8y/o for DIPG
DIPG Presenting Symptoms

- Cranial nerve deficits
- Long-track signs
- Ataxia

- Hydrocephalus is rare

- Duration of symptoms is usually days to weeks, can be up to 3 (6) months.
Classic MRI Findings

- Dark on T1
- Bright on T2 or FLAIR
- Appear to have a border between pons and medulla
- Appears to envelope the basilar artery
- Not diffusely enhancing (can have an enhancing focus though)
- Should involve >50% (66%) of the pons
- Typically ventral pons > dorsal pons
Diffuse Pontine Glioma Imaging

DIPG

Normal
Treatment of DIPG

- Surgical resection
- Chemotherapy
- Radiation

- Focal wide field photon radiation therapy
  - 5400-5940cGy given in 30-33 fractions at 180cGy/day
  - Proton therapy not indicated

- Radiation dose escalation
- Hypofractionation
Outcome of DIPG

Fig. 2. Event-Free Survival Comparison of ACNS0126 and CCG-9941.
Treatment of DIPG Over the Last 30 Years

- >250 clinical trials (based on MRI)
  - Pre-XRT chemotherapy
  - Post-XRT chemotherapy
  - Pre and Post-XRT chemotherapy
  - Immunotherapy
  - Biologic therapy
  - Radiation sensitizers
  - Anti-angiogenic therapies
  
- Everything but the kitchen sink

- All of these patients died without benefit

- When we say a trial was negative, it was more than negative
  - Patients suffered toxicities with no benefit
• In many of these trials, combine HGG and DIPG patients.
  – In many ways, these are different diseases

• In many of these trials, combine DIPG with other brainstem tumors
  – These are usually different diseases
Pre-Clinical Models of DIPG

- Derived from cells of glial origin, predominantly, supratentorial adult GBM

- Autopsy cases
- Upfront biopsy of atypical brain stem tumors
- Upfront biopsy of classic DIPG
  - New models now available
    - GEMM
Whole Genome Copy Number Alterations in Pediatric DIPG vs Pediatric HGAs

9 autopsy and 2 up-front biopsy cases

Whole genome view of copy number alterations for pediatric diffuse intrinsic pontine gliomas (DIPGs) versus pediatric supratentorial high-grade astrocytomas (HGAs) highlighting the distinct genetic characteristics of DIPGs. Patients are arranged sequentially with patient 1 at the top and patient 11 at the bottom. Red: copy number gain, blue: copy number loss.

Zarghooni M et al. JCO 2010;28:1337-1344 (Hawkins lab)
Whole Genome Copy Number Alterations in Pediatric DIPG vs Pediatric LGGs

37 autopsy and 7 up-front biopsy cases

Copy-number abnormalities in diffuse intrinsic pontine glioma (DIPG). (A) Heat map showing segmentation analysis of normalized data from Affymetrix SNP 6.0 arrays to identify copy-number gains (red) and losses (blue) in 43 DIPGs and eight brainstem low-grade gliomas (LGGs). Chromosome positions are indicated along y-axis and separated by dashed line. Histologic subtypes are indicated across top. Scale bar shows color gradient to indicate copy number. Comparison of frequencies of most common large-scale genomic
Histone H3 Mutations in DIPG

Table 1  Frequency of recurrent somatic mutations in DIPG and GBM

<table>
<thead>
<tr>
<th>Gene</th>
<th>Amino acid change</th>
<th>DIPG(^a) (%)</th>
<th>non-BS-PG(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H3F3A</td>
<td>p.Lys27Met</td>
<td>30 (60)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>H3F3A</td>
<td>p.Gly34Arg</td>
<td>0</td>
<td>5 (14)</td>
</tr>
<tr>
<td>HIST1H3B</td>
<td>p.Lys27Met</td>
<td>9 (18)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>All H3</td>
<td></td>
<td>39 (78)</td>
<td>13 (36)</td>
</tr>
</tbody>
</table>

\(^a\)For DIPGs, total \(n = 50\). \(^b\)For non-BS-PGs, total \(n = 36\).
Clinical Trials for Histone Mutations

• Many epigenetic modifiers under study
• Histone deacetylase (HDAC) inhibitors
  – Valproic acid
  – SAHA (Vorinostat)
  – Panobinostat
• Histone demethylases
  – Jumanji 3 and 4 inhibitors
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
• Pilot assessment of biologic material to see if quality will support detailed analyses.
Molecular Profile of Newly-Diagnosed DIPG

20 up-front biopsy cases of DIPG

Results of the CGH array with Agilent 44K Whole Human Genome Array G4410B are indicated by the ratio of chromosomal imbalance; values above 1.5 were considered as amplifications and those below 0.3 were considered as losses. IHC for p53 (DO-7 antibody) was graded in a semi-quantitative way (cut-off 10%).

Grill et al. (Kieran) Pediatric Blood and Cancer 58(4):489-91. Epub 2011 Dec 20
DIPG is Different From GBM

B: Heatmap of the 712 most differentially expressed genes between DIPG, midline and hemispheric tumors, selected using the moderated t-test of limma package of Bioconductor.

23 up-front biopsy cases of DIPG

Two Distinct Molecular Subgroups

- Mesenchymal/pro-angiogenic
- Oligodendroglial
  - PDGFR-A driven
New Targets in DIPG

Fontabasso et al (Kieran), Nature Genetics, April 6, 2014
## Targets in Pediatric DIPG/HGG

<table>
<thead>
<tr>
<th></th>
<th>H3F3A</th>
<th>HIST1H3B/HIST1H3C</th>
<th>TP53</th>
<th>FGFR1</th>
<th>ACVR1</th>
<th>PDGFRA</th>
<th>PIK3CA/PIK3R1/PTEN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H3F3A</strong></td>
<td>0.0002</td>
<td>0.0331</td>
<td>0.5515</td>
<td>0.0015</td>
<td>0.5515</td>
<td>0.6488</td>
<td></td>
</tr>
<tr>
<td><strong>HIST1H3B/HIST1H3C</strong></td>
<td>0.0002</td>
<td>0.0586</td>
<td>1.000</td>
<td>0.0002</td>
<td>1.000</td>
<td>0.1023</td>
<td></td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>0.0331</td>
<td>0.0586</td>
<td>0.0154</td>
<td>0.0154</td>
<td>0.1445</td>
<td>0.2538</td>
<td></td>
</tr>
<tr>
<td><strong>FGFR1</strong></td>
<td>0.5515</td>
<td>1.000</td>
<td>0.0154</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td><strong>ACVR1</strong></td>
<td>0.0015</td>
<td>0.0002</td>
<td>0.0154</td>
<td>1.000</td>
<td>1.000</td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td><strong>PDGFRA</strong></td>
<td>0.5515</td>
<td>1.000</td>
<td>0.1445</td>
<td>1.000</td>
<td>1.000</td>
<td>0.5536</td>
<td></td>
</tr>
<tr>
<td><strong>PIK3CA/PIK3R1/PTEN</strong></td>
<td>0.6488</td>
<td>0.1023</td>
<td>0.2538</td>
<td>1.000</td>
<td>0.048</td>
<td>0.5536</td>
<td></td>
</tr>
</tbody>
</table>

- **Red**: Mutually exclusive
- **Blue**: Associated/Concurrent

Submitted for publication
New Targets in Pediatric DIPG

- **H3.3 K27M / TP53**
- **H3.1 K27M / ACVR1**
- **H3.1 K27M / TP53**
- **H3.3 K27M**
- **H3.3 K27M / TP53**
- **H3.3 K27M / FGFR1 / NF1 / H3.3 WT**
- **H3.3 G34R/V / TP53 / ATRX**
- **IDH1 / TP53 / ATRX**
- **SETD2 / IDH1**
- **H3.3 WT**

Brain regions:

- **Cerebral hemispheres**
  - H3.3 K27M / TP53
  - H3.3 K27M / FGFR1 / NF1
  - H3.3 WT

- **Thalamus**
  - H3.3 K27M / TP53
  - H3.3 K27M / TP53

- **Cerebello-pontine area**
  - H3.1 K27M / ACVR1
  - H3.1 K27M / TP53
  - H3.3 K27M
  - H3.3 K27M / TP53

- **Spinal cord**
  - H3.3 K27M / TP53
ACVR1 and DIPG

Taylor et al (Grill), Nature Genetics, April 6, 2014
What Do We Know About ACVR1

Taylor et al (Grill), Nature Genetics, April 6, 2014
Fibrodysplasia Ossificans Progressiva

Fibrodysplasia ossificans progressiva
Drug Distribution and CNS Penetration
Matrix Assisted Laser Desorption Ionization (MALDI) Mass Spectrometry Imaging

Confirmation of Compound Identity by MS/MS with MALDI TOF/TOF
ACVR1 Inhibitor CNS Penetration
What Does This Mean for Patients with DIPG?

• Histone demethylase and deacetylase inhibitors are being studied (BBB penetration)

• Targeting PI3k, PDGFR, ACVR1 mutations in newly diagnosed DIPG
  – New clinical trial
Participating Institutions

• DFCI, Boston
• UCSF, San Francisco
• Children’s Memorial, Chicago
• CHLA, Los Angeles
• Jacksonville Children’s, FL
• Seattle Children’s, WA
• Denver Children’s, CO
• Johns Hopkins, MD
• Miami Children’s, FL
• Wayne State, MI

• Washington Univ, St Louis
• NYU Med Center, NY
• Doernbecher, OR
• CHOA, Atlanta
• Univ of MN, Minneapolis
• UT Southwestern, Dallas
• Louisville Children’s, KY
• Univ South Carolina, SC
• Cook Children’s, Fort Worth
• Duke University, NC
Acknowledgments

UCSF
• Nalin Gupta and Mike Prados

McGill University
• Nada Jabado

DFCI/BCH
• Susan Chi, Peter Manley, Pratiti Bandopadhayay,
• Lilly Goumnerova,
• Keith Ligon,
• Hayley Malkin, Lianne Greenspan
Acknowledgments

• Patients and their families
• Funding agencies
  – Zach Carson DIPG Foundation
  – Ellie Kavalieros Foundation
  – Mikey Czech Foundation
  – Prayers From Maria Foundation
  – Hope for Caroline Foundation
  – Ryan Harvey DIPG Fund
  – DIPG Collaborative
  – The Cure Starts Now Cancer Foundation