Cognitive Outcomes in Children Experiencing Seizures during Treatment for Acute Lymphoblastic Leukemia

Principal Investigator
Stephanie L. Nassar, M.A.

Co-Investigators
Heather M. Conklin, Ph.D.
Jason M. Ashford, M.S.
Yinmei Zhou, M.S.
Cheng Cheng, Ph.D.
Wilburn E. Reddick, Ph.D.
John O. Glass, Ph.D.
Sima Jeha, M.D.
Ching-Hon Pui, M.D.
Cognitive Correlates of Seizures in Healthy Kids

- Short-term memory deficits
- Visual spatial problems
- Poorer attention
ALL and Seizure Activity

3% to 13% experience seizures

Katelyn

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Cognitive Correlates of Seizures in Children with CNS Relapse

Seizure Activity

(\( r = -0.42, p < .01^{*} \))

Performance IQ

Mulhern et al., 1987

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Seizures and Risk

- Recurrent seizures
- Disrupted intellectual development

Rao et al., 2002
CNS Effects of Chemotherapy

CNS-directed therapy

Lower cerebral white matter volumes

Poorer cognitive outcomes

Ashford et al., 2010; Reddick et al., 2006

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Rationale

• Known prevalence, onset, prognosis, and treatment of seizures during ALL therapy

• Abundant data on cognitive outcomes of children treated for ALL

however…
Rationale

• Cognitive outcomes of children treated for ALL who experience therapy-related seizures is unknown

• Improve
  – Treatment planning
  – Monitoring
  – Caregiver education
Study Objective 1

- To estimate the **rate** of seizure occurrence in children undergoing therapy for ALL and identify **relevant factors** associated with risk.
Study Objective 2

• To assess change in neuropsychological status of children who experienced treatment-related seizures.
Study Objective 3

• To characterize post-treatment cognitive performance among children experiencing treatment-related seizures by comparing to:
  1. normative sample
  2. patients not experiencing seizures on protocol
Study Objective 4

• To compare prevalence of leukoencephalopathy between children experiencing treatment-related seizures and similarly treated patients without a history of seizures.
Study Design - Participants

- St. Jude Total Therapy XV (TOTXV) patients
  - Experienced therapy-related seizures ($n = 19$)
  - Matched to two patients on protocol not experiencing seizures ($n = 38$)
  - Gender
  - Race
  - Age at treatment
  - Treatment intensity
Study Design - Methods

• Retrospective, three time point cognitive assessment with parental questionnaires

  - End of 6-week continuation (baseline)
  - Week 120 continuation
  - 2 years post therapy completion

• MRI exams

  - End of 6-week remission induction
  - Week 7 continuation
  - Week 120 continuation
## Study Design - Methods

<table>
<thead>
<tr>
<th>Area</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual functioning</td>
<td>Wechsler Estimated/Full Scale IQ</td>
</tr>
<tr>
<td>Academic achievement</td>
<td>WIAT Basic Reading</td>
</tr>
<tr>
<td></td>
<td>WIAT Math Reasoning</td>
</tr>
<tr>
<td>Attention, working memory, processing speed</td>
<td>Wechsler Indices</td>
</tr>
<tr>
<td></td>
<td>Conners’ CPT</td>
</tr>
<tr>
<td>Parent report of behavioral problems</td>
<td>Conners’ Parent Rating Scales</td>
</tr>
</tbody>
</table>

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Study Design - Methods

• MRI Exams
  – Imaging classification

Normal  Leuko
### Patient Demographics at Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Seizure Cases</th>
<th>Cohort Match1</th>
<th>Cohort Match2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>57</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>0.9996</td>
</tr>
<tr>
<td>Mean</td>
<td>8.26</td>
<td>8.27</td>
<td>8.26</td>
<td>8.23</td>
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</tr>
<tr>
<td>SD</td>
<td>4.72</td>
<td>4.80</td>
<td>4.81</td>
<td>4.82</td>
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<tr>
<td>Median</td>
<td>7.66</td>
<td>7.21</td>
<td>8.00</td>
<td>7.66</td>
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</tr>
<tr>
<td>Range</td>
<td>2.07-18.73</td>
<td>2.07-18.73</td>
<td>2.09-17.12</td>
<td>2.14-18.73</td>
<td></td>
</tr>
</tbody>
</table>

^ Analysis of Variance
## Patient Demographics at Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Total (n=57)</th>
<th>Case (n=19)</th>
<th>Match1 (n=19)</th>
<th>Match2 (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>42(73.7)</td>
<td>14(73.7)</td>
<td>13(68.4)</td>
<td>15(78.9)</td>
</tr>
<tr>
<td>Black</td>
<td>14(24.6)</td>
<td>5(26.3)</td>
<td>5(26.3)</td>
<td>4(21.1)</td>
</tr>
<tr>
<td>Other</td>
<td>1(1.8)</td>
<td>0 (0)</td>
<td>1(5.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Gender [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>39(68.4)</td>
<td>13(68.4)</td>
<td>13( 68.4)</td>
<td>13(68.4)</td>
</tr>
<tr>
<td>F</td>
<td>18(31.6)</td>
<td>6(31.6)</td>
<td>6( 31.6)</td>
<td>6(31.6)</td>
</tr>
<tr>
<td><strong>Initial Risk [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>21(36.8)</td>
<td>7(36.8)</td>
<td>7(36.8)</td>
<td>7(36.8)</td>
</tr>
<tr>
<td>Std/High</td>
<td>36(63.2)</td>
<td>12(63.2)</td>
<td>12(63.2)</td>
<td>12(63.2)</td>
</tr>
<tr>
<td><strong>Current Risk [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>20(35.1)</td>
<td>7(36.8)</td>
<td>7(36.8)</td>
<td>6(31.6)</td>
</tr>
<tr>
<td>Std/High</td>
<td>37(64.9)</td>
<td>12(63.2)</td>
<td>12(63.2)</td>
<td>13(68.4)</td>
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<tr>
<td><strong>Pearson's Chi-Square Test</strong></td>
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</tbody>
</table>

Results – Objective 1 – Seizure Rate

- **Rate** of Grade 3 seizure or higher
  - 1-year: 3.21% ± 0.79%
  - 2-year: 3.82% ± 0.86%

Cumulative Incidence of Grade 3 Seizure or Higher on TOTXV

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Results – Objective 1 – Seizure Risk

• No relevant factors associated with risk
• No differences between therapeutic doses
  – HDMTX, DEX, ITHMA
## Results – Objective 1 – Seizure by Tx Phase

- **Induction** and **Consolidation** phases

<table>
<thead>
<tr>
<th>Phase</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Treatment</td>
<td>1</td>
<td>5.26%</td>
</tr>
<tr>
<td>Induction</td>
<td>5</td>
<td>26.32%</td>
</tr>
<tr>
<td>Consolidation</td>
<td>5</td>
<td>26.32%</td>
</tr>
<tr>
<td>Continuation Weeks 1-6</td>
<td>1</td>
<td>5.26%</td>
</tr>
<tr>
<td>Continuation Weeks 10-16</td>
<td>3</td>
<td>15.79%</td>
</tr>
<tr>
<td>Continuation Weeks 48-95</td>
<td>1</td>
<td>5.26%</td>
</tr>
<tr>
<td>LR Continuation Weeks 20-47</td>
<td>2</td>
<td>10.53%</td>
</tr>
<tr>
<td>HR Continuation Weeks 21-47</td>
<td>1</td>
<td>5.26%</td>
</tr>
</tbody>
</table>
Results – Objective 2 – Neuropsychological Status for Children with Seizures

Neuropsychological Change Across Treatment Among Children Experiencing Seizures

[Bar chart showing standard score changes across different domains such as EIQ, FSIQ, Reading, Math, FFD, PSI, DS Total Omissions, Hit RT, Learning, Psychosomatic, Impuls-Hyper, Hyperactive for Baseline (Week 6), Week 120, and 2 Years Post.]
Results – Objective 3 – Baseline Comparisons

Seizure-Norm-NonSz Comparisons at Baseline (Week 6)

- EIQ
- Reading
- Math
- Omissions
- Hit RT
- Learning
- Psychosomatic
- Impuls-Hyper
- Hyperactive

\( p = .052 \)

$T$ Score

- Seizure
- NonSz
Results – Objective 3 – Week 120 Comparisons

Seizure-Norm-NonSz Comparisons at Week 120

T Score

Standard Score

EIQ  FSIQ  Reading  Math  FFD  PSI  DS Total  Omissions  Hit RT  Learning  Psychosomatic  Impuls-Hyper  Hyperactive

T Score

Red: Seizure  Blue: NonSz
Results – Objective 3 – 2 Year Post Comparisons

Seizure-Norm-NonSz Comparisons at 2 Years Post

[Bar chart showing comparisons between Seizure and NonSz groups for various categories such as EIQ, FSIQ, Reading, Math, FFD, PSI, DS Total, Omissions, Hit RT, Learning, Psychosomatic, Impuls-Hyper, and Hyperactive. The chart includes stars indicating significant differences.]
## Results – Objective 4 – Imaging Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Classification</th>
<th>Seizure Group</th>
<th>NonSz Group</th>
<th>p-value Fisher’s Exact Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End of 6-week remission induction</strong></td>
<td>Leuko</td>
<td>2 (15.38)</td>
<td>1 (2.94)</td>
<td>0.1812</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>11 (84.62)</td>
<td>33 (97.06)</td>
<td></td>
</tr>
<tr>
<td><strong>Week 7 continuation</strong></td>
<td>Leuko</td>
<td>9 (56.25)</td>
<td>4 (12.90)</td>
<td>0.0043*</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>7 (43.75)</td>
<td>27 (87.10)</td>
<td></td>
</tr>
<tr>
<td><strong>Week 120 continuation</strong></td>
<td>Leuko</td>
<td>5 (38.46)</td>
<td>2 (6.06)</td>
<td>0.0138*</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>8 (61.54)</td>
<td>31 (93.94)</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

• Seizure incidence was low

• Children with therapy-related seizures demonstrated worse performance than children without seizures
  – Attention and working memory tasks
  – Same pattern at two years post, with PSI deficits
  – Full scale IQ at two years post therapy completion

• Imaging suggests early neurotoxicity
  – Trend for baseline differences on EIQ
Limitations and Future Directions

- Prospective, longitudinal study
- Baseline measurement
- Sophisticated imaging (e.g., DTI)
Funding

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Research Team

• Heather Conklin, Ph.D.
  • Jason Ashford, M.S.
  • Kellie Clark, M.S.
  • Robyn Howarth, Ph.D.
  • Karen Martin-Elbahesh, M.S.
  • Jane Schreiber, Ph.D.
  • Tori Willard, Ph.D.
  • Shannon Thomas-Lohrman, M.S.
• Yinmei Zhou, M.S.
Questions or Comments?

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