Overview of the Effects of Cancer Treatment on Cognitive Impairment in Children

No Conflicts of Interest to Disclose
Cancer Treatment Effects on Cognitive Impairment in Children

• **Neurocognitive function**
  – Multidimensional concept comprised of domains reflecting a healthy brain
    • Attention
    • Learning
    • Information processing speed
    • Visual-spatial skills
    • Psychomotor skills
    • Executive function
      – working memory
      – inhibition & self control
      – concept formation
      – planning & organization
What are the Consequences of CNS-Directed Therapy for Children?
Cancer Treatment Effects on Cognitive Impairment in Children

• Neurodevelopmental and academic problems
  – Memory
  – Visual spatial abilities
  – fine motor speed
  – attention
  – processing speed
  – academic achievement

• Common & challenging consequence of CNS-directed treatment
  – 20 to 60% of ALL survivors
  – 40 to 100% of brain tumor survivors
Cancer Treatment Effects on Cognitive Impairment in Children

- **Secondary consequences on**
  - behavioral adjustment
    - 41% at risk for internalizing problems
  - psychological well being (anxiety, depression)
  - social & adaptive skills
  - vocational success
  - leadership skills
  - independent living
  - quality of life
Cancer Treatment Effects on Cognitive Impairment in Childhood ALL

One in 330 children diagnosed with cancer by age 20

One in 530 young adults 20 to 39 years of age is a childhood cancer survivor

Most prevalent cancer among children & adolescents is acute lymphoblastic leukemia

once fatal

5 year survival approaches 90%
Improved Survival from Childhood ALL

Use of multi-agent chemotherapy

Know risk factors for recurrence
minimal residual disease
treatment intensity matched to recurrence risk

Aggressive CNS-directed treatment for subclinical disease in the brain
primary site of initial disease relapse
Risk Factors for Treatment-related Cognitive Problems

- Younger age at diagnosis
  - associated with worse outcomes in some studies
  - Greater decline in verbal working memory among children < 5 years of age at diagnosis
- Sex differences in rate of development of white matter tracks may different patterns of cognitive problems
- Treatment Intensity
  - faster rate of decline in visual spatial skills among children treated with intrathecal and intravenous methotrexate compared to those treated with only intrathecal therapy
- Ethnicity
  - Hispanic ethnicity robustly associated with neurotoxicity risk after accounting for sex, age at diagnosis, and ALL risk stratification
Percent of Subjects Performing 1 or 1.5 Standard Deviation Below Norm

- Visual Motor Integration
- Bead Memory
- Memory for Sentences
- Number Letter Identification
- Finger Windows
- WRAML2 Composite
- Purdue dominant
- Purdue non-dominant
- Purdue both
- Letter-word identification
- Calculation

% performing ≥ 1 SD below the norm

% performing ≥ 1.5 SD below the norm
Factors of Attention Score Distribution

- Focus
- Hyperactivity/Impulsivity
- Sustain
- Vigilance
n = 71; * significantly below age-adjusted norms
Cognitive Abilities Impact Academic Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Visual Motor Integration</th>
<th>Visual Memory</th>
<th>Verbal Memory</th>
<th>Fine Motor Abilities</th>
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</thead>
<tbody>
<tr>
<td>Letter/Word Identification</td>
<td>$r = 0.748$</td>
<td>$r = 0.624$</td>
<td>$r = 0.534$</td>
<td>$r = 0.465$</td>
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<td></td>
<td>$p &lt; 0.001$</td>
<td>$p &lt; 0.001$</td>
<td>$p &lt; 0.001$</td>
<td>$p &lt; 0.001$</td>
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<tr>
<td>Calculation</td>
<td>$r = 0.536$</td>
<td>$r = 0.340$</td>
<td>$r = 0.321$</td>
<td>$r = 0.290$</td>
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<tr>
<td></td>
<td>$p &lt; 0.001$</td>
<td>$p = 0.015$</td>
<td>$p = 0.020$</td>
<td>$p = 0.040$</td>
</tr>
</tbody>
</table>
Why do Children with ALL have Long-Term Neurodevelopmental Problems?
CNS Directed Chemotherapy Model of Neurologic Injury: Oxidative Stress & Apoptosis
Glutathione (GSH)

- Predominant anti-oxidant synthesized within cell (cytosol)
- Present in
  - reduced (GSH) form
  - major brain antioxidant
  - oxidized (GSSG) form
- Ratio of GSH/GSSG normally >100 but can be < 4 during oxidative stress
- GSH efflux from cell occurs in response to increase in ROS
Changes in CSF GSH during CNS Directed Treatment

Diagnosis
Induction
Post-Induction
Maintenance

nM

Total GSH Peptide
Initial Reduced GSH
Mean GSSG
Glutathione (GSH/GSSG) Ratio over Time

Diagram showing the mean ratio of GSH/GSSG over time, with labels for Diagnosis, Induction, Post-Induction, and Maintenance.
Caspase Enzymes

• Cysteine-dependent aspartate-specific protease enzymes
  – 14 have been identified

• Initiate or execute apoptosis
  – caspase 8 (extrinsic pathway)
  – caspase 9 (intrinsic pathway)
  – both activate caspase 3

• Caspase 3 and 7 execute apoptotic cell death
CSF Caspase Activity by Treatment Phase

![Graph showing luminescence units for Caspase 3/7, Caspase 8, and Caspase 9 across different treatment phases: Diagnosis, Induction, Post-Induction, Continuation.](image-url)
Caspase 3/7 is Associated with Cognitive Abilities at End of Treatment

<table>
<thead>
<tr>
<th>Mean Caspase 3/7</th>
<th>Beery VMI Memory</th>
<th>Bead Memory</th>
<th>Sentence Memory</th>
<th>WRAML2 attention/concentration</th>
<th>WRAML2 finger window</th>
<th>WRAML2 number letter</th>
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</thead>
<tbody>
<tr>
<td>Induction</td>
<td>r = -.354</td>
<td>r = -.430</td>
<td>r = -.381</td>
<td>r = -.330</td>
<td>r = -.144</td>
<td>r = -.274</td>
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<tr>
<td></td>
<td>p = 0.006</td>
<td>p = 0.001</td>
<td>p = 0.003</td>
<td>p = 0.010</td>
<td>p = 0.158</td>
<td>p = 0.027</td>
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<tr>
<td>Post Induction</td>
<td>r = -.41</td>
<td>r = -.189</td>
<td>r = -.290</td>
<td>r = -.324</td>
<td>r = -.248</td>
<td>r = -.196</td>
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<tr>
<td></td>
<td>p = 0.002</td>
<td>p = 0.097</td>
<td>p = 0.022</td>
<td>p = 0.011</td>
<td>p = 0.041</td>
<td>p = 0.087</td>
</tr>
</tbody>
</table>

Active GSH export from the cell an early event in apoptosis through intrinsic or extrinsic pathways
Increase in extracellular GSH initiating event for caspase activation
Increases in caspase 8 (extrinsic pathway) and caspase 9 (intrinsic pathway) activity activates caspase 3/7
Can Cognitive and Academic Abilities be Preserved in Children with ALL?
Improving Academic Outcomes: Math Intervention

Determine if Math Intervention prevents declines in academic math scores in children with ALL.
Improving Academic Outcomes: Math Intervention

- Children consented after diagnosis confirmed and therapy initiated
- Random assignment to intervention or standard care
- Neurocognitive evaluations completed for all subjects at baseline, post-intervention and 12 months later
- Children in intervention group received 40 hours of math enhancement skills using a “multiple representations” approach over 12 months
- Parents of children in both groups received feedback on child’s neurocognitive evaluation performance
Change over Time in Nonverbal Working Memory

F [2, 29] = 5.53, p <= .009
Change over Time in Applied Mathematical Problem Solving Skills

Significant group by time interaction
F [2, 29] = 12.47, p <0.001
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Sample Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conklin, et al.</td>
<td>Investigate efficacy and adverse effects of methylphenidate (MPH) among survivors of ALL or a brain tumor with learning impairment.</td>
<td>Childhood cancer survivors (n = 122) treated with chemotherapy and/or CNS-directed radiation</td>
<td>Therapeutic effect of MPH relative to placebo significant only for the ink naming time of the Stroop Word-Color Association Test</td>
</tr>
<tr>
<td>Butler, et al.</td>
<td>Test Cognitive Remediation Program (CRP) efficacy on academic achievement, brief focused attention, working memory, memory recall, and vigilance</td>
<td>Survivors of a childhood malignancy (n = 161) that involved CNS disease and/or treatment to the CNS</td>
<td>Significant improvement in academic achievement; modest effect size; subjects in intervention group incorporated more metacognitive strategies and manifested improved attention (parent report)</td>
</tr>
<tr>
<td>Patel, et al.</td>
<td>Evaluate an intervention teaching compensatory learning and problem solving skills to improve cognitive, academic, and social functioning</td>
<td>Children (n = 12; 6 males and 6 females) treated with CNS-directed therapy for brain tumors (9), leukemia (2) or CNS histiocytes (1).</td>
<td>Statistically significant improved scores on the WJR Writing Samples standard score and the Social Skills Rating System standard score. Scores on all measures changed approximately $\frac{1}{2}$ SD indicating improved performance</td>
</tr>
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<tr>
<td>Hardy, et al.</td>
<td>Pilot test a computerized cognitive training program for feasibility, acceptability, and effect on attention and working memory</td>
<td>Survivors (n = 9) of ALL (3) or brain tumors (6) between 10 and 17 years of age</td>
<td>Significant increase in Digit-Span Forward subscale of the working memory index and significant decrease in Cognitive Problems Index (parent report)</td>
</tr>
</tbody>
</table>
Conclusions/Future Directions

- Apoptosis and oxidative stress have a role in CNS treatment-related neurologic injury
- Caspase enzymes serve as a biomarker of neurocognitive decline
- Potential efficacy of behavioral neuro-protective interventions
- Growing evidence for “accelerated aging” in some pediatric cancer survivors.
- Could cognitive decline represents an accelerated aging cognitive aging phenotype?
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