Managing Behavioral Changes During Treatment for Acute Lymphoblastic Leukemia (ALL)

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November 4, 2016
How *should* we measure outcomes?

Hunger et al., Journal of Clinical Oncology, 2012
Overview

• Results of multi-site prospective study

• Interventions

• Future directions
Design

- 31 sites in the U.S. and Australia
- Prospective and longitudinal
- Ancillary study within frontline therapeutic trial
- Parent surveys at 4 time points
- 170 patients enrolled

*CHILDREN'S ONCOLOGY GROUP*

The world's childhood cancer experts

*OUR MISSION*

To cure and prevent childhood and adolescent cancer through scientific discovery and compassionate care.
Eligibility

• Diagnosis of standard risk ALL
• Enrolled on COG AALL0331 at participating site
• Age at diagnosis 2.0-9.9 years
• Parent literate in English or Spanish
AIMS

• Determine how health-related quality of life (HRQOL) outcomes in children with ALL vary during therapy

• Identify predictors of HRQOL outcomes that will inform future intervention studies, and the critical time points when such interventions should occur
Children’s Oncology Group AALL0331
Clinical Trial Schema

Induction

- Standard Consolidation 28 days
- Intensified Consolidation 56 days

Standard IM
- Augmented IM

DI

Maintenance

~1 mo post-dx

~6 mo post-dx

~12 mo post-dx

~3 mo off-rx

T1
T2
T3
T4
### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Participants (n = 160)</th>
<th>Nonparticipants (n = 34)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>4.9 (SD: 2.9)</td>
<td>4.1 (SD: 2.2)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>School Level</strong></td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Preschool (2-4)</td>
<td>87 (54.4)</td>
<td>23 (67.7)</td>
<td></td>
</tr>
<tr>
<td>School age (5-9)</td>
<td>73 (45.6)</td>
<td>11 (32.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>Male</td>
<td>83 (51.9)</td>
<td>16 (47.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>77 (48.1)</td>
<td>18 (52.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>108 (67.5)</td>
<td>16 (47.1)</td>
<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>11 (6.8)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>27 (16.9)</td>
<td>8 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14 (8.8)</td>
<td>9 (26.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>Standard CS/standard IM-DI</td>
<td>43 (26.9)</td>
<td>8 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Intensified CS/standard IM-DI</td>
<td>51 (31.9)</td>
<td>11 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Standard CS/augmented IM-DI</td>
<td>37 (23.1)</td>
<td>6 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Intensified CS/augmented IM-DI</td>
<td>29 (18.1)</td>
<td>9 (26.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>131 (81.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spanish</td>
<td>18 (11.3)</td>
<td></td>
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<tr>
<td>Other</td>
<td>2 (1.3)</td>
<td></td>
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</tr>
<tr>
<td>Missing</td>
<td>9 (5.5)</td>
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<tr>
<td><strong>Maternal Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than college</td>
<td>55 (34.4)</td>
<td></td>
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<tr>
<td>At least some college</td>
<td>93 (58.1)</td>
<td></td>
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</tr>
<tr>
<td>Missing</td>
<td>12 (7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Family Income</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $50,000</td>
<td>72 (45.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ $50,000</td>
<td>55 (34.4)</td>
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<tr>
<td>Missing</td>
<td>33 (20.7)</td>
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</tr>
</tbody>
</table>
Survey Instruments

• Behavioral Assessment System for Children- 2nd Ed (BASC-2)
  – Anxiety and depression

• Pediatric Quality of Life Inventory (PedsQL 4.0)
  – Physical, emotional, and social functioning

• Pediatric Quality of Life Inventory 3.0 Cancer Module
  – Nausea, pain, procedure anxiety, treatment anxiety during therapy

• Family Assessment Device-General Functioning scale (FAD-GF)
  – Family functioning
First Year: Anxiety in at risk/clinical range

Myers et al., Cancer, 2014
First year: Depression in at risk/clinical range

Myers et al., Cancer, 2014
Predictors of emotional distress in the first year in multivariate analysis (repeated measures analysis)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unhealthy family functioning</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Unhealthy family functioning</td>
<td>2.24</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Hispanic ethnicity</td>
<td>3.35</td>
<td>0.009</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unhealthy family functioning</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Unhealthy family functioning</td>
<td>2.40</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Unmarried parents</td>
<td>2.36</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Not significant:* sex, age, income, maternal education, treatment arm

Myers et al., Cancer, 2014
Anxiety in at risk/clinical range three months post-therapy

Kunin-Batson et al., Cancer, 2016
Depression in at risk/clinical range three months post-therapy

Kunin-Batson et al., Cancer, 2016
### Predictors of emotional distress 3 months post-therapy (multivariate analysis)

<table>
<thead>
<tr>
<th></th>
<th>Anxiety</th>
<th>Depression</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>none</td>
<td>1. Unhealthy family functioning</td>
<td>OR=2.62, p=0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Spanish speaking</td>
<td>OR=6.28, p=0.047</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Unhealthy family functioning</td>
<td>OR=4.43, p=0.03</td>
</tr>
</tbody>
</table>

*Not significant:* sex, age, ethnicity, income, maternal education, treatment

Kunin-Batson et al., Cancer, 2016
Earlier emotional distress predicts post-therapy distress

- **Anxiety symptoms in at risk/clinical range at 3 months post-therapy predicted by:**
  - Anxiety at 1 month (OR= 4.1, p=0.02)
  - Anxiety at 6 months (OR=5.5, p=0.009)
  - Anxiety at 12 months (OR=6.2, p=0.005)

- **Depression symptoms in at risk/clinical range at 3 months post-therapy predicted by:**
  - Depression at 6 months (OR=7.9, p=<0.001)
  - Depression at 12 months (OR=3.7, p<0.01)

Kunin-Batson et al., Cancer, 2016
Cancer PedsQL scale scores in the first year

Dupuis et al., Cancer, 2016
Cancer PedsQL scale scores in the first year

Mean PedsQL cancer module subscale score

- **Pain**
  - 1 mo vs 6 mo: P<0.0001
  - 1 mo vs 12 mo: P<0.0001
  - 6 mo vs 12 mo: P=0.0389

- **Nausea**
  - 1 mo vs 6 mo: P<0.0001
  - 1 mo vs 12 mo: P=0.0085
  - 6 mo vs 12 mo: P<0.0001

Dupuis et al., Cancer, 2016
Quality of Life: Trends in Impaired Functioning

Mitchell et al., International Journal of Cancer, 2016
Stresses in first year: parents’ work

Lau et al., Pediatric Blood and Cancer, 2014
Stresses in first year: family life

Lau et al., Pediatric Blood and Cancer, 2014

- Changed plan and decided not to have more children
- Divorced or separated
Stresses in first year: Housing

Lau et al., Pediatric Blood and Cancer, 2014
Summary of findings

• Substantial proportions of children with ALL experience emotional distress

• Treatment for ALL is disruptive to the entire family

• Unhealthy family functioning and Hispanic ethnicity are associated with greater emotional distress

• Patient experience elevated levels of anxiety and depression symptoms post-therapy

• Early emotional distress predicts later distress
Psychosocial support is already part of our treatment culture

- Social workers
- Child life specialists
- Nurses
- Chaplaincy
- Art therapy
- Therapy dogs
- Psychologists
- Psychiatrists
- Health Educators
- “Buddy” programs
- Complementary therapy
- Specialty camps
- Hospital schools
- Support groups
... And Clowns!

Therapeutic clowns in pediatrics: a systematic review and meta-analysis of randomized controlled trials

Kannan Sridharan\textsuperscript{1} • Gowri Sivaramakrishnan\textsuperscript{2}
Challenges to effective interventions

• Access to mental health expertise
• Cost of supportive care services
• Scheduling conflicts due to competing medical care priorities
• Different developmental needs
• Feasibility and generalizability across sites
The Psychosocial Assessment Tool (PAT) by Kazak and colleagues

- 5-10 minutes by parent
- Web-based or paper and pencil
- 4th grade reading level
- Multiple languages
- Categorizes family psychosocial risk
  - Universal (low)
  - Targeted (medium)
  - Clinical (high)

Acta Oncologica, 2015; 54: 574-580
Conceptual framework for the PAT

Pediatric Psychosocial Preventive Health Model

CLINICAL/TREATMENT
- Consult behavioral health specialist.
- Intensify psychosocial services.
- Address impact on medical treatment.

TARGETED
- Monitor child/family distress and risk factors.
- Provide interventions specific to symptoms or adherence needs.

UNIVERSAL
- Provide psychoeducation and family-centered support.
- Screen for indicators of higher risk.

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Impact of the PAT on psychosocial care

• Identified 7.2 risks/family compared to 2.7/family after “usual” psychosocial screening at Children’s Hospital of Philadelphia (n=96 patients)
  
  Kazak et al. Psychooncology 2011

• Providing PAT results to the medical team improved risk levels, parental anxiety, child behavior, and quality of life 6 months later in RCT (n=67 patients)
  
  Barrera et al. Psychooncology 2014
Cognitive Behavioral Therapy

• Hands-on, practical approach to problem-solving
• Goal is to change patterns of thinking or behavior that are behind people’s difficulties
• Efficacy in children and parents
• Usually in person and by trained mental health professionals
• Board game “ShopTalk” (Weiner et al. 2011)
Problem-Solving Skills Training for mothers by Sahler and colleagues

- Cognitive-behavioral approach
- 8 one-hour individual in-person sessions with mothers
- Associated with less negative emotions in mothers in 2 randomized trials
- Efficacy: Spanish > English speaking mothers
- Maintained 3 months post-intervention
E-health interventions in children with cancer

- Smartphone in addition to traditional therapy
  Smartphone training (n=197) did not enhance Problem-Solving Skills Training in mothers (Askins et al. 2009)

- Videotelephone support for newly diagnosed patients and families
  Ongoing randomized control trial (n=162) of 12 week intervention (Bensink et al. 2007)

- Online group-based cognitive behavioral therapy
  Three 90 minute sessions in parents (n=47) showed feasibility but not efficacy (Wakefield et al. 2016)
Strategies at your site

• Systematically triage patients

• Identify a champion who leads the psychosocial program

• Psychosocial multidisciplinary conference
  – Care planning and coordination
  – “Matchmaker” of needs with resources
  – MDs, nurses, child life, SW, mental health experts
Future Directions

- Ongoing prospective study of 600 children on current ALL trial to replicate findings and understand impact of reducing maintenance therapy

- Planning intervention study for upcoming therapeutic study in Childrens Oncology Group

- Education and advocacy to champion expanded psychosocial support in clinical practice
Acknowledgements

• We are grateful to our patients and their families

• NIH grants to the Children’s Oncology Group including CA98543, CA1880886, U10 CA98413, CA180899 and a Community Oncology Research Program grant U10CA095861

• Investigators
  Kelly Maloney          William Carroll
  Leonard Mattano       Naomi Winick
  Stephen Hunger        L. Lee Dupuis
  Lillian Sung          Hannah-Rose Mitchell
  Alicia Kunin-Batson   Regina Myers

• **Statisticians:** Meenakshi Devidas and Xiaomin Lu
Participating Sites for COG AALL0331 HRQOL Ancillary Study

- Children’s Hospital Medical Center, Akron, OH
- Children’s Hospital at the Cleveland Clinic, Cleveland, OH
- Children’s Hospital Colorado, Aurora, CO
- Children’s Hospital of Central California, Madera, CA
- Children’s Hospital and Clinics of Minnesota, Minneapolis and St. Paul, MN
- Children’s Hospital, New Orleans, LA
- Children’s Hospital of Pittsburgh, Pittsburgh, PA
- Seattle Children’s Hospital, Seattle, WA
- Helen DeVos Children’s Hospital, Grand Rapids, MI
- Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE
- East Tennessee Children’s Hospital, Knoxville, TN
- Hackensack University Medical Center, Hackensack, NJ
- Randall Children’s Hospital at Legacy Emanuel, Portland, OR
- Loma Linda University Medical Center, Loma Linda, CA
- Midwest Children’s Cancer Center, Milwaukee, WI
- Nevada Cancer Research Foundation
- Princess Margaret Hospital for Children, Perth, Australia
- St. Vincent Hospital, Regional Cancer Center, Green Bay, WI CCOP
- Packard Children’s Hospital at Stanford, Stanford, CA
- SUNY Upstate Medical University, Syracuse, NY
- St. Joseph’s Children’s Hospital of Tampa, Tampa, FL
- University of Alabama at Birmingham Hospital, Birmingham, AL
- University of Florida Academic Health Center, Gainesville, FL
- University of Minnesota Medical Center, Fairview, Minneapolis, MN
- Children’s Hospital, University of Mississippi Medical Center, Jackson, Mississippi
- University of New Mexico Children’s Hospital, Albuquerque, New Mexico
- University of Texas Southwestern Medical Center, Dallas, TX
- American Family Children’s Hospital, University of Wisconsin Children’s Hospital, Madison, WI
- Children’s Hospital at Vanderbilt, Nashville, TN