Toxicity Management: Supportive Care Options for Children with Leukemia

Lillian Sung, MD, PhD

Speaker bio

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Dr. Lillian Sung is a Full Professor and Senior Scientist at The Hospital for Sick Children, Toronto, Ontario, Canada. She is certified in the specialties of pediatrics, infectious diseases, hematology and clinical investigation. She completed a PhD in Clinical Epidemiology from the University of Toronto in 2004. She has a clinical research program focused on supportive care for children with cancer. Her methodological focus is on randomized and observational trials, meta-analysis, and patient-reported outcomes. She is the principal investigator on multiple operating grants from the National Institutes of Health (NIH), Canadian Cancer Society Research Institute and the Canadian Institutes of Health Research.

Dr. Sung is the Chair of Cancer Control and Supportive Care in the Children’s Oncology Group (COG). COG is the largest pediatric cancer clinical trials consortium and includes over 200 member institutions. She is the co-PI on the NCI Community Oncology Research Program (NCORP) Research Base grant which supports the Cancer Control and Supportive Care program within COG. Dr. Sung is also the co-PI on an NIH R25 grant to support the Clinical Research Training Institute, sponsored by the American Society of Hematology.
Toxicities of Leukemia Therapy

Treatment-Related Mortality and Acute Leukemia

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POGO Conference
November 4, 2016
Outline

• Introduction and Challenges to Defining TRM
• Creation of TRM Definitions
• Population-based Epidemiology of TRM
• Conclusions
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• Introduction and Challenges to Defining TRM

• Creation of TRM Definitions

• Population-based Epidemiology of TRM

• Conclusions
Importance of TRM

- Devastating outcome of cancer diagnosis
- TRM versus disease-related death fundamental to identifying best strategy to improve survival in pediatric cancer
  - If TRM main cause of death – enhanced supportive care, possible reduction therapy
  - If disease main cause of death – treatment intensification or novel approaches
Areas of Inconsistency

• How TRM defined
  - Specific definition
    ? Exclude based upon timing
    ? Exclude based upon cause of death
  - Inclusion post relapse or HSCT

• Cause of death
  - For example, death due to infection or bleeding
# Expectation on AAML1031

<table>
<thead>
<tr>
<th>Date of Death:*</th>
<th>MM/DD/CCYY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Cause of Death:*</td>
<td></td>
</tr>
<tr>
<td>- Due to this disease</td>
<td></td>
</tr>
<tr>
<td>- Due to protocol treatment</td>
<td></td>
</tr>
<tr>
<td>- Unknown</td>
<td></td>
</tr>
<tr>
<td>- Due to other cause, specify</td>
<td></td>
</tr>
<tr>
<td>Contributing cause(s) of death:*</td>
<td></td>
</tr>
<tr>
<td>- Due to this disease</td>
<td></td>
</tr>
<tr>
<td>- Due to protocol treatment</td>
<td></td>
</tr>
<tr>
<td>- Due to other cause, specify</td>
<td></td>
</tr>
<tr>
<td>- None</td>
<td></td>
</tr>
</tbody>
</table>

- Check all that apply.

If “due to other cause, specify” is selected in either of the above questions, describe the cause of death not listed among the choices. If not, please leave this question blank.

Describe cause of death:

TEXT
Outline

- Introduction and Challenges to Defining TRM
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Systematic Reviews

Aim: To describe how TRM has been defined in randomized therapeutic studies or any study design in which TRM was an outcome
Systematic Review Methods

- Two focused on TRM:
  - Pediatric acute leukemia
  - Pediatric lymphoma, solid tumors and brain tumors

- Eligibility Criteria:
  - Pediatric studies
  - RCTs evaluating anti-cancer treatment OR
  - Any study type focused on TRM
  - Studies published ≥ 1990
Flow of Study Identification/Selection

Literature Search

Leukemia

- Full articles retrieved for detailed evaluation: n = 124
- Satisfied eligibility criteria: n = 51
  - RCTs: n = 41
  - TRM Outcome: n = 10

Lymphoma/Solid/Brain Tumors

- Full articles retrieved for detailed evaluation: n = 131
- Satisfied eligibility criteria: n = 67
  - RCTs: n = 62
  - TRM Outcome: n = 5
Key Findings

- Two concepts - TRM and early deaths

• TRM defined in:
  - 9/51 (18%) leukemia
  - 0/72 (0%) lymphoma, solid or brain tumor

- Early death defined in:
  • 8/51 (16%) leukemia
  • 1/72 (1%) lymphoma, solid or brain tumor
## Specific TRM Definitions

<table>
<thead>
<tr>
<th>Leukemia</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from causes other than progressive disease where failures at the end of two courses, relapses and deaths from progressive disease were competing events.</td>
<td>3</td>
</tr>
<tr>
<td>Induction death or death in first complete remission. Excluded deaths prior to start treatment and following SCT.</td>
<td>3</td>
</tr>
<tr>
<td>Death after day 42 in those in complete remission and those between day 42 and 150 who did not respond to treatment. <em>Excluded relapse patients.</em></td>
<td>2</td>
</tr>
<tr>
<td>Death unrelated to refractory or progressive disease occurring before day 42 or any death after day 42. <em>Excluded relapse patients.</em></td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma/Solid Tumor/Brain Tumor</td>
<td>0</td>
</tr>
</tbody>
</table>
# Specific Early Death Definitions

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leukemia</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 42 days of treatment start</td>
<td>4</td>
</tr>
<tr>
<td>Within 60 days of diagnosis</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 14 days from start of therapy</td>
<td>1</td>
</tr>
<tr>
<td>Before 8 days</td>
<td>1</td>
</tr>
<tr>
<td>Before response to therapy could be established</td>
<td>1</td>
</tr>
<tr>
<td><strong>Lymphoma/Solid Tumor/Brain Tumor</strong></td>
<td></td>
</tr>
<tr>
<td>Within 42 days of treatment start</td>
<td>1</td>
</tr>
</tbody>
</table>
Summary

- TRM only defined in acute leukemia, not solid tumors or brain tumors
- Two concepts: TRM and early deaths
- Tremendous variability across studies
- Can use identified definitions to dissect elements contributing to TRM delineation
Elements Used to Define TRM Identified in Systematic Review

- Relapse
- Progressive disease at death
- Remission at death
- HSCT
- Induction failure
- Date end of induction
- Day of therapy
Focus Group

Aim: To agree upon a definition of TRM and development of a system for cause of death attribution

Alexander Lancet Oncology 2016
Underlying Assumptions

• Intent broad purpose, applicable to populations and trials

• No perfect system and clinicians will disagree
  - Goal to create reproducible system

• Ideal definition:
  - Easy to abstract, reliable, minimizes subjectivity
  - Does not rely upon physician actions (variable)
  - Can be applied across different co-operative groups
  - Can be applied across different diseases
  - Adaptable e.g. relapse or HSCT
Consensus Decisions in Defining TRM

• Not use deaths in induction
  - Variable between diseases, groups

• Not use deaths within a set number of days
  - Not helpful for identifying cause of death
  - Dependent on specific protocols

• Allow deaths before starting cancer treatment
  - Receipt of cancer treatment provider-driven
  - May benefit from enhanced supportive care
Elements Used to Define TRM Identified in Systematic Review

- Relapse
- Progressive disease at death
- Remission at death
- HSCT
- Induction failure
- Date end of induction
- Day of therapy
Consensus Definition

Death defined as TRM:
- Diagnosed with cancer
- Absence of progressive disease at death

- Could include or exclude relapse or HSCT
- No requirement to have received cancer treatment
- No element of time
- Defined “treatment” broadly
Cause-of-Death Attribution

• Patients commonly have multiple events contributing to death e.g. leukemia, infection, metabolic disturbance, etc.
  - System must allow multiple main causes

• In general, no guidance provided to data abstractors or clinicians

• Reliability poor
Cause-of-Death – ICD10 Philosophy

• “all those diseases, morbid conditions or injuries which either resulted in or contributed to death and the circumstances …which produced any such injuries”

• Purpose ensure all relevant information recorded and ensure recorder not selective about which condition listed

• Should not include symptoms and modes of dying, such as heart failure or respiratory failure
TRM Attribution Approach

- Eliminate primary versus secondary/contributing

- List all important events proximal to death
  - 2 weeks

- Certainty of attribution
  - Definite/Probable vs Possible
**Creation**

- Began with ICD10 categories

- Initial draft used CTCAE v4.0.
  - If grade 4/5 - definite/probable
  - If grade 3 - possible
  - If < grade 3, do not include

- Refined draft in series of working group calls
<table>
<thead>
<tr>
<th>Cause of Death Attribution *14 days prior to death</th>
<th>Probable</th>
<th>Possible</th>
<th>Not Present</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td>Clinically or radiographically documented infection with associated microbiologically documented organism</td>
<td>Acute symptomatic intracranial hemorrhage demonstrated by imaging or pathology</td>
<td>Clinically or radiographically documented infection without associated microbiologically documented organism</td>
</tr>
<tr>
<td><strong>Hemorrhage</strong></td>
<td>Acute symptomatic intracranial hemorrhage demonstrated by imaging or pathology</td>
<td>Acute symptomatic pulmonary hemorrhage without demonstration by imaging or pathology</td>
<td></td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td>Acute symptomatic intracranial thrombosis or embolism demonstrated by imaging or pathology</td>
<td>Acute symptomatic pulmonary thrombosis or embolism without demonstration by imaging or pathology</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac System</strong></td>
<td>Acute symptomatic atrial fibrillation excluding sinus tachycardia/bradyarrhythmia demonstrated by echocardiogram</td>
<td>Acute symptomatic atrial fibrillation excluding sinus tachycardia/bradyarrhythmia without demonstration by echocardiogram</td>
<td></td>
</tr>
<tr>
<td><strong>Immune Mediated</strong></td>
<td>Acute allergic reaction or anaphylaxis with symptomatic bronchospasm or edema/angioedema or hypotension</td>
<td>Acute symptomatic hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome or cytokine-release syndrome</td>
<td>Stable graft versus host disease</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>Acute symptomatic central nervous system necrosis demonstrated by imaging or electroencephalography</td>
<td>Acute symptomatic central nervous system necrosis without demonstration by imaging or electroencephalography</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td>Acute symptomatic hemorrhage or stroke demonstrated by imaging or pathology</td>
<td>Acute symptomatic hemorrhage or stroke without demonstration by imaging or pathology</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
<td>Acute symptomatic respiratory distress leading to ventilator support including intubation, or other mechanisms of pressure support including BiPAP and CPAP</td>
<td>Acute symptomatic respiratory distress without ventilator support</td>
<td></td>
</tr>
<tr>
<td><strong>GI System</strong></td>
<td>Acute clinically diagnosed hepatic dysfunction associated with increased conjugated bilirubin &gt; 10x ULN or high ammonia &gt; 2.5x ULN or INR &gt; 2.5x ULN</td>
<td>Acute clinically diagnosed hepatic dysfunction associated with increased conjugated bilirubin &gt; 1.5 to ≤10x ULN or INR &gt; 1.5 to ≤2.5x ULN or ammonia &gt; 1.5 to ≤2.5x ULN</td>
<td></td>
</tr>
<tr>
<td><strong>Renal System</strong></td>
<td>Acute kidney injury with dialysis/renal replacement therapy planned or received</td>
<td>Acute clinically diagnosed hepatic dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>External Causes</strong></td>
<td>Unintentional injury (e.g. accident)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Validation of TRM Designation System

Aim: To validate the TRM algorithm in a random sample of 30 deaths occurring between Jan 1, 2003 and Dec 31, 2012 at SickKids

- Two CRAs independently reviewed cases and classified TRM (yes vs no) and cause-of-death
- Two pediatric oncologists performed same evaluation
- Hypothesized $k \geq 0.60$ between CRA and physician TRM classification
- Qualitatively evaluated cause-of-death attribution
TRM Classification Reliability and Validity

Clinician Reliability
Kappa 0.84 (95% CI 0.63 to 1.00)

CRA Reliability
Kappa 0.83 (95% CI 0.60 to 1.00)

Criterion Validity
Kappa 0.92 (95% CI 0.78 to 1.00)
Summary of TRM

- 9/30 (30%) TRM

- Number of definite/probable attributions
  – median 2 (range 2 to 5)
Outline

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Aim: To describe the proportion of deaths due to TRM and to identify risk factors and probable causes of TRM in a population-based cohort for children who died Jan 1, 2003 and Dec 31, 2012.
Provincial Review of Deaths

- POGO – all 5 tertiary care pediatric cancer centers in Ontario
- Almost complete capture up to 14 years of age
- All HSCT procedures - SickKids

*https://ec.gc.ca/cas-aqhi/55517B0A-DA24-455F-93DD-0FF5314C9A00/AQ_prov_ON_400.jpg
Designation Procedure

- 6 CRAs trained and evaluated with 10 randomly chosen cases with correct response determined by 2 pediatric oncologists
- Required 9/10 correct TRM designations before could review independently
- CRAs travelled to each site
- TRM designation did not censor at relapse or HSCT
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Overall Conclusions and Next Step

• Created new TRM definition – reliable, feasible and flexible

• In Ontario, TRM - 26% pediatric cancer deaths

• Next steps – describe TRM rate:
  - Among newly diagnosed cancer in Ontario
  - Disseminate new system
TRM Training

http://lab-stg.research.sickkids.ca/sung
Acknowledgements

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TRM Working Group Members

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Wim Tissing MD - Netherlands