Cardiac Risk Factors in Survivors of Childhood Cancer

Paul Nathan MD, MSc
Director, AfterCare Program
Division of Haematology/Oncology
The Hospital for Sick Children, Toronto
Conflicts

Nothing to declare
Learning objectives

• To understand the long-term cardiac outcomes in survivors of childhood cancer

• To identify the risk factors for late cardiac morbidity in this population

• To appreciate the options for preventing or mitigating late cardiac morbidity
The 5 year survival rate for childhood acute lymphoblastic leukemia (ALL) was 4% in 1962 and today it is 94%.

That is what research does.

September is Childhood Cancer Awareness Month.
Multiple chronic medical conditions (severe, life threatening or death)

Armstrong et al. ASCO 2012
Relative risk of severe or life threatening health conditions

<table>
<thead>
<tr>
<th>Chronic Condition</th>
<th>Relative Risk (compared to siblings)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>15.1</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>10.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Oeffinger et al. NEJM 2006
Late mortality

Recurrence | 58%
New cancer | 19%
Heart disease | 7%
Lung disease | 3%
External causes | 7%

Armstrong et al. JCO 2009
Cardiovascular toxicity in childhood cancer survivors

- 10-fold increased risk of dying from cardiac causes
  - Leading non-cancer cause of premature mortality
  - *Anthracycline* chemotherapy and cardiac *radiation* are the 1º culprits

- Cardiomyopathy/CHF
- Coronary artery disease (and stroke)
- Pericarditis
- Valve disease
- Arrhythmias
A. Arrhythmia
B. Pericardial disease
C. CAD
D. Valvular disease

Khanna et al.
Mechanisms of anthracycline cardiotoxicity

Anthracyclines: (e.g. doxorubicin, daunorubicin) → 50%

- Reactive oxygen species
- Topoisomerase (TopIIβ knockouts protected)
- Impaired mitochondrial biogenesis
- Mitochondrial iron accumulation
- Transcription factors: aryl carbon receptor, hypoxia inducible factor
Mitochondrial dysfunction, Sarcopenia, Loss of myocytes, Myocardial thinning, Increased wall stress, Decreased contractile reserve, Damage to remaining myocytes, Mitochondrial dysfunction, Sarcopenia, Late cardiac dysfunction, ↓ SF/EF, Early cardiac dysfunction, ↓ strain, Cardiac remodeling, ↓ LVPWT, ↓ thickness:dimension, Reactive oxygen species, Anthracycline exposure, Topoisomerase II, Compensatory pathways, Fibrosis.
Potential for intervention to prevent anthracycline cardiomyopathy

- Limit exposure
- Less toxic analogues
- Bolus vs. infusion
- Cardio-protectants

- Healthy lifestyle
- Manage modifiable RF (hypertension, diabetes)
- Pharmacologic
  - ACE-I
  - β-blockers

- Pharmacologic
  - ACE-I
  - β-blockers

Armenian, Gelehrter, Chow: Cardiol Res Pract 2012
Primary prevention: Who is at risk?

1. Cumulative dose
2. Young age
3. Chest radiation
4. Gender (female)
5. Prior cardiac disease
6. Acute cardiac toxicity
7. Bolus vs. infusion?
8. Genetics
Relationship between cumulative anthracycline exposure and risk of cardiomyopathy
Primary prevention:
Evolution of cancer treatment to spare the heart

Armstrong NEJM 2016
Evolution of cancer treatment to spare the heart
Individual Prediction of Heart Failure Among Childhood Cancer Survivors


Table 3. CHF Risk Scores and Corresponding Model Discrimination and Predictive Power*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Simple Model†</th>
<th>Standard Model</th>
<th>Heart Dose Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Age at diagnosis, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5-9</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10-14</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>≥ 15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Anthraoycline, mg/m²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any</td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>—</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>100-249</td>
<td>—</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥ 250</td>
<td>—</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Chest or heart RT, Gy‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any</td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5-14</td>
<td>—</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>15-34</td>
<td>—</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>≥ 35</td>
<td>—</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Risk Group</td>
<td>Risk Score</td>
<td>Cumulative Incidence at 40 years</td>
<td>RR vs. siblings [vs. group above]</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>----------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;3</td>
<td>0.5 (0.2-0.7)</td>
<td>1.8 [ - ]</td>
</tr>
<tr>
<td>Moderate</td>
<td>3-5</td>
<td>2.4 (1.8-3.0)</td>
<td>12.1 [6.6]</td>
</tr>
<tr>
<td>High</td>
<td>≥6</td>
<td>11.7 (8.8-14.5)</td>
<td>41.5 [3.4]</td>
</tr>
</tbody>
</table>
Targeted cancer therapy

Genetic variability

Treatment sensitivity of the tumor

Predisposition to toxicity in the patient

Personalized cancer therapy
Genetic predisposition to cardiac toxicity

Drug transport
SLC28A3, ABCB1, ABCB4, ABCC1, MRP2

↑ Anthracycline

CBR3

Dox-quinone
→ Dox-ol

Dox-semiquinone*

O₂⁻/H₂O₂

NAD(P)H oxidase multi-enzyme complex

RAC2 NCF4 CYBA

HAS 3 HA

Anti oxidant activity

ROS

↑ ROS

Mitochondrial dysfunction

Myocyte apoptosis

Maladaptive LV remodeling

ECM and remodeling

HAS 3 HA

Heart failure

Decreased myocardial contractility

↑ cTnT

> 1 isoforms of cTnT

CELF4 CELF4 protein

CELF-mediated alternative splicing of cTnT

Loss of Fe Homeostasis

Aconitase/IRP1

SickKids

Slide courtesy of Dr. Eric Chow
Canadian Pharmacogenomics Network for Drug Safety: Combined clinical and SNP model

Clinical variables
- Age @ treatment
- Dose
- Gender
- Radiation therapy
- Ethnicity

SNPs (9)
- SLC28A3 (solute carrier family)
- ABCB4, ABCC1 etc.

Visscher. JCO 2012
Secondary prevention: Surveillance

<table>
<thead>
<tr>
<th>Anthracycline Dose*</th>
<th>Radiation Dose**</th>
<th>Recommended Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>&lt; 15 Gy or none</td>
<td>No screening</td>
</tr>
<tr>
<td></td>
<td>≥ 15 - &lt; 35 Gy</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td>≥ 35 Gy</td>
<td>Every 2 years</td>
</tr>
<tr>
<td>&lt; 250 mg/m²</td>
<td>&lt; 15 Gy or none</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td>≥ 15 Gy</td>
<td>Every 2 years</td>
</tr>
<tr>
<td>≥ 250 mg/m²</td>
<td>Any or none</td>
<td>Every 2 years</td>
</tr>
</tbody>
</table>

*Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33.

**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76.
Surveillance guidelines: Effective? Cost effective?

Cost-Effectiveness of the Children’s Oncology Group Long-Term Follow-up Screening Guidelines for Childhood Cancer Survivors at Risk for Treatment-Related Heart Failure

F. Lennie Wong, PhD; Smita Bhatia, MD, MPH; Wendy Landler, PhD, RN; Liton Francisco, BS; Wendy Leisenring, ScD; Melissa M. Hudson, MD; Gregory T. Armstrong, MD; Ann Mertens, PhD; Marilyn Stovall, PhD; Leslie L. Robison, PhD; Gary H. Lyman, MD, MPH; Steven E. Lipshultz, MD; and Saro H. Armenian, DO, MPH

Results of Base-Case Analysis: The COG guidelines versus no screening have an ICER of $61,500, extend life expectancy by 6 months and QALYs by 1.6 months, and reduce the cumulative incidence of heart failure by 18% at 30 years after cancer diagnosis. However, less frequent screenings are more cost-effective than the guidelines and maintain 80% of the health benefits.

Conclusion: The COG guidelines could reduce the risk for heart failure in survivors at less than $100,000/QALY. Less frequent screening achieves most of the benefits and would be more cost-effective than the COG guidelines.
Targeting cardiovascular risk factors in survivors

Cardiovascular Disease Risk Factors:

- Obesity
- Medical Rx for hypertension, dyslipidemia, diabetes

Cardiovascular Risk Factor Cluster (CVRFC):

- Any three or more risk factors

Data from CCSS courtesy of Dr. G Armstrong
Cardiovascular Risk Factors: Prevalence

- **Hypertension**
  - Survivor (39%)
  - Sibling (28%)

- **Dyslipidemia**
  - Survivor (28%)
  - Sibling (18%)

- **Diabetes**
  - Survivor (9%)
  - Sibling (5%)

- **Obesity**
  - Sibling (35%)
  - Survivor (20%)
Coronary Artery Disease

- CVRFC alone: RR=7.9
- Chest RT alone: RR=5.0
- Chest RT + CVRFC: RR=39.8

p<0.001

Congestive Heart Failure

- CVRFC alone: RR=5.2
- Chest RT alone: RR=3.7
- Chest RT + CVRFC: RR=26.3

p=0.002
<table>
<thead>
<tr>
<th>Condition</th>
<th>Hypertension alone</th>
<th>Chest RT alone</th>
<th>Chest RT + Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>8.7</td>
<td>4.8–15.8</td>
<td>5.3</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>12.2</td>
<td>7.4–20.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Valve Abnormality</td>
<td>8.1</td>
<td>1.6–40.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>9.2</td>
<td>3.7–22.7</td>
<td>2.8</td>
</tr>
</tbody>
</table>

P<0.001 for all comparisons between Chest RT alone and Chest RT + Hypertension
Secondary prevention: Pharmacologic

- Current trial of carvedilol in survivors who received >250 mg/m² anthracycline but normal function
- Failed study of perindopril in survivors with reduced LVPW
Treatment of Stage B/C CHF

- Retrospective review:
  - 18 children treated with enalapril (12 asymptomatic, 6 symptomatic)
  - Initial improvement, but all deteriorated b/w 6-10 years
  - By 6 years, all who had started with CHF had died or had transplant
  - 7/12 asymptomatic patients dead or CHF by 10 years

Lipshultz et al. JCO 2002
Conclusions

1. Cardiovascular disease is a significant cause of morbidity and mortality in childhood cancer survivors

2. Clinical risk prediction models useful but imperfect

3. Genomics, better imaging (and maybe biomarkers) may improve ability to predict future cardiac morbidity

4. In survivors → focus on lifestyle, modifiable risk factors etc.
Questions