Cardiac Disease in Childhood Cancer Survivors: From Bench to Bedside and Beyond

Department of Pediatrics
Grand Rounds
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Gregory J. Aune, MD, PhD
Greehey Children’s Cancer Research Institute
University of Texas Health Science Center San Antonio

Disclosure
Gregory J. Aune, MD, PhD discloses the following relationships with commercial companies:
Confidentiality Agreement with Azaya Therapeutics for providing liposomal doxorubicin at no cost

Learning Objectives
• Identify the common severe late effects seen in long-term survivors of pediatric cancer
• Review the literature regarding cardiac disease in survivors and list currently available strategies for prevention
• Discuss the use of animal models to overcome limitations in the development of new chemotherapy agents and predicting long-term toxicity

From Bench to Bedside
Clinical Studies Identify Alarming Incidence of Severe Cardiac Disease in Childhood Cancer Survivors

Clinical Research
• Protection
• Diagnosis
• Prevention

Preclinical Research
• Animal models
• Cellular and molecular studies

Clinical Research
• Survivorship Cohort
• Cardiac MRI Study

Preclinical Research
• Evaluate protective strategies
• Identify new molecular targets

Identify the common severe late effects seen in long-term survivors of pediatric cancer
• Types of cancer and outcomes in children
• Common Late Health Effects
• Frequency of Debilitating or Life-threatening Late Health Affects
• Late Mortality

Childhood Cancer Incidence
• Approximately 15,000 new patients each year in the United States
• Most common cancers are leukemia followed closely by brain tumors
So where does that leave us?

- 5 year survival rates for all newly diagnosed patients > 75%
- In 2010, there were an estimated 325,000 long-term survivors of pediatric cancer in the U.S. (In Texas: 30,000)

Toxicity

Acute Toxicity

- Well known and recognized by providers and lay persons
- Nausea, vomiting, hair loss, and bone marrow suppression
- Radiation pneumonitis and skin burns

Late Toxicity

- Less obvious to medical providers and lay persons
- Affect virtually every organ system
- Recognition of the severity and scope is largely the product of epidemiological research conducted in the 21st century
**Childhood Cancer Survivor Study (CCSS)**

- Funded by National Cancer Institute in 1994
- Self-report questionnaire sent to 20,720 pediatric cancer survivors and 6,000 matched sibling controls
- Patients had cancer diagnosis between the years 1970-1986
- An enormous amount of observational data regarding late effects has been published

**Life-threatening and Debilitating Late Effects**

- 2/3 experience at least one late effect
- 1/4 experience a severe late effect, that may be life threatening

Oeffinger et al., NEJM. 2004.

**Chronic Health Conditions in Adult Survivors of Childhood Cancer**


<table>
<thead>
<tr>
<th>Condition</th>
<th>Number (n=2286)</th>
<th>Number (n=692)</th>
<th>Median (5th-95th)</th>
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<tbody>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
<td></td>
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<tr>
<td>Heart failure</td>
<td>202</td>
<td>73</td>
<td>(3.7-44.7)</td>
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<tr>
<td>Lung cancer</td>
<td>40</td>
<td>16</td>
<td>(6.2-47.2)</td>
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<tr>
<td>Other pulmonary</td>
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<td>24</td>
<td>(1.7-22.5)</td>
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<td><strong>Cardiac</strong></td>
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<tr>
<td>Heart failure</td>
<td>135</td>
<td>48</td>
<td>(3.0-44.9)</td>
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<tr>
<td>Lung cancer</td>
<td>26</td>
<td>11</td>
<td>(6.2-47.2)</td>
</tr>
<tr>
<td>Other cardiac</td>
<td>92</td>
<td>24</td>
<td>(1.7-22.5)</td>
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<tr>
<td><strong>Skeletal</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Arthritis</td>
<td>114</td>
<td>46</td>
<td>(3.9-45.9)</td>
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<tr>
<td>Myositis</td>
<td>85</td>
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<td>(6.8-45.9)</td>
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<td>Osteoporosis</td>
<td>24</td>
<td>10</td>
<td>(1.4-24.8)</td>
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<td><strong>Endocrine</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Growth failure</td>
<td>137</td>
<td>48</td>
<td>(3.0-44.9)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>44</td>
<td>17</td>
<td>(3.9-45.9)</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Cognitive impairment</td>
<td>44</td>
<td>17</td>
<td>(3.9-45.9)</td>
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<td>Psychologic impairment</td>
<td>59</td>
<td>23</td>
<td>(3.9-45.9)</td>
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<td>Motor impairment</td>
<td>59</td>
<td>23</td>
<td>(3.9-45.9)</td>
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<td><strong>Second cancers</strong></td>
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<td></td>
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<tr>
<td>Second malignancies</td>
<td>26</td>
<td>11</td>
<td>(6.2-47.2)</td>
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<tr>
<td>Second primary malignancies</td>
<td>24</td>
<td>10</td>
<td>(6.8-45.9)</td>
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</table>

Outcomes of 1,743 adult survivors of childhood cancer with a median age of 32

**Clinical Assentment of Health Outcomes Among Adults Treated for Childhood Cancer**


By age 50

- 83.5% will develop valve disorder
- 21.6% will develop cardiomyopathy

**Affected Organ Systems**

- CNS – cognitive, psych, motor
- Endocrine – growth, fertility
- Skeletal – growth, orthopedic problems
- Cardiac
- Pulmonary
- Second cancers

**Late mortality in childhood cancer survivors**
Cause-specific late mortality among 5-year survivors of childhood cancer: The childhood cancer survivor study. The cause of death was obtained for 2,534 5-year survivors of pediatric cancer. The overall standardized mortality ratio (SMR) was 8.4 (CI 8.0-8.7). Cause-specific SMR increased for:
- Secondary malignancies
- Cardiac
- Pulmonary
- Other medical causes

Review the literature regarding cardiac disease in survivors and list currently available strategies for prevention
- Types of cardiac disease and causative treatments
- Prevention strategies

Cardiovascular late effects
- Valvular heart disease- chest XRT
- Cardiomyopathy- anthracyclines (doxorubicin, daunorubicin, mitoxantrone)
- Coronary artery disease- XRT, anthracyclines
- Heart attack
- Sudden cardiac death
- Stroke- neck XRT
- Anthracycline chemotherapies are unequivocally linked to myocardial and vascular damage

Cardiovascular disease
- Numerous studies have documented excess cardiovascular disease risk in survivors of pediatric cancer
- Survivors are 5-10 times more likely than sibling controls to have heart disease
- SMR for cardiac death is 7-8.2 times higher in cancer survivors
- Full extent of the problem may not be realized due to relative young age of the existing survivor cohort

Prevention strategies
- Proposed reduction in cardiotoxicity by giving anthracyclines as a continuous infusion vs. bolus dosing
  - Peak serum dose less resulting in less cardiotoxicity
- Liposomal anthracycline preparations promoted by pharmaceutical industry as less cardiotoxic
- Cardioprotective therapeutics
Liposomal Preparations

- Some studies in adult breast cancer patients indicate reduced cardiotoxicity
- Expensive
- Have not been utilized or systematically studied in the pediatric population

Cardioprotective Therapeutics

- Only approved medication for prevention of acute anthracycline-induced cardiotoxicity is the iron-chelator dexrazoxane (Zinecard)
- In numerous studies has been shown to decrease elevation of troponins during anthracycline infusion and abrogate dysfunction measured by ECHO

For all of these prevention strategies

- Efficacy in terms of long-term cardiac outcomes is unknown
- Cellular and molecular mechanisms are difficult to study - minimal access to heart tissue

Discuss the use of animal models to overcome limitations in the development of new chemotherapy agents and predicting long-term toxicity

- Identify gaps in existing preclinical research
- Describe a novel mouse model
- Identify cellular and histologic changes in myocardium
- Review cell culture studies focusing on collagen production

Gap in Research

- Preclinical animals models used to study anthracycline cardiac toxicity do not use young animals and do not account for the long latent period
  - use adult animals
  - typically evaluate outcome no more than 8 weeks following exposure (most commonly one week)
Gap in Research

- The vast majority of preclinical research focuses on myocyte responses
  - fibroblasts and immune cells which mediate the injury response have been largely overlooked
  - vascular endothelial cells and cardiac progenitor cells are also adversely affected

Describe a novel mouse model to study long-term cardiac outcomes after chemotherapy and radiation

Overall Hypothesis:
In mice, acute doxorubicin exposure during cardiac development initiates persistent collagen synthesis by cardiac fibroblasts that culminates in cardiac fibrosis and heart failure

Laboratory Model:
Doxorubicin Exposure in Pediatric Mice

- 5 weekly IP injections of doxorubicin
- Major outputs: 1) echocardiography 2) LV tissue archive 3) plasma archive 4) survival

2 Week-old Mice

ECHO and Necropsy
Identify the acute histologic and cellular changes induced by anthracyclines in myocardium.
Cell culture studies focusing on collagen production

Cell culture studies focusing on collagen production
Fibroblast p53 Response in vivo

Proposed Model

Beyond Barriers in Developing New Chemotherapy Agents
- Less than 5% of oncology drugs selected for testing in humans successfully achieve FDA approval with up to 30% dropping out at the registration phase (very late in clinical development)
- Cardiovascular toxicity is the most frequent adverse toxicity resulting in withdrawal from the market
- Cardiovascular toxicity accounts for only 9% of attrition during phase I
- Identification of cardiovascular toxicity needs to receive more emphasis during early development of new chemotherapy agents

Summary
- Long-term survivors of pediatric cancer patients are a growing population that faces an array of severe medical problems
- Cardiac disease is a leading cause of early mortality in this population
- Preclinical studies focusing on the mechanisms by which chemotherapy and radiation damage the pediatric heart are lacking
- Acute exposure to anthracyclines in young mice elicits cardiac dysfunction and extracellular matrix deposition
- Doxorubicin induces increased collagen expression and secretion in cardiac fibroblasts

Future Directions
- Evaluate the long-term cardiac protective efficacy of liposomal doxorubicin and dexrazoxane
  - Hyundai Corporation
  - St. Baldrick’s Foundation
- Identify changes in myocardial gene expression in mice with defects transcription elongation
  - NCI R21
- Elucidate the underlying molecular mechanisms that regulate collagen production in response to doxorubicin
- *in vitro* methodology to conduct high-throughput screens identifying inhibitors of collagen production

“Problems cannot be solved with the same mind set that created them.”
Albert Einstein
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QUESTIONS?