The Tell-tale Heart: Late Effects in Pediatric Cancer Survivors

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Disclosure

• I have no financial conflicts of interest to disclose

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

September is

Childhood Cancer Awareness Month

Learning Objectives

• With respect to the heart, review the known cell-specific molecular events induced by the well-recognized cardiotoxic chemotherapy agents
• Recognize the urgent need to develop laboratory models to investigate the underlying molecular mechanisms mediating chemotherapy and radiation-induced cardiotoxicity

Overall Objectives

• Recognize late effects as an increasingly important consideration in pediatric oncology
• Understand that our knowledge regarding late effects is largely observational; there is an urgent need for basic science efforts focused on understanding the molecular mechanisms of both acute and late toxicities
Childhood Cancer Incidence
- Approximately 15,000 new patients each year in the United States
- Most common cancers are leukemia followed closely by brain tumors

Survival by Year

Survival by Cancer Type

So where does that leave us?
- 5 year survival rates for all newly diagnosed patients > 75%
  - all pediatric cancers and all-comers
- In 2010, there were an estimated 325,000 long-term survivors of pediatric cancer in the U.S. (In Texas: 30,000)
- 1 in 500 young adults are cancer survivors

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
• Patient had cancer diagnosis between the years 1970-1986
• An enormous amount of observational data regarding late effects has been published

Limitations of the CCSS

• Self reported data and much of it has not been validated
• Not the most ethnically diverse population -- mostly Caucasian
• Importantly for San Antonio and South Texas survivors, the cohort studied lacks Hispanics

CCSS Literature

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

Chronic Health Conditions in Adult Survivors of Childhood Cancer
Learning Objective #1

Identify the common severe late effects seen in long-term survivors of pediatric cancer

Affected Organ Systems

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

Pulmonary

- Pulmonary fibrosis
- bleomycin, chest XRT

Endocrine

- Obesity
- Diabetes- total body XRT or abdomen + chest XRT
- Growth problems- cranial XRT
- Ovarian failure- SCT or XRT to abdomen
- Hypothyroidism- XRT to neck
- Infertility
- Decrease bone mineral density

Secondary Malignancies

- Risk of second tumor is higher than non-treated at all time points post treatment
- Skin cancers (non-melanoma) are particularly common
- Related to both specific chemotherapy agents and sites of radiation

Cause-Specific Late Mortality Among 5-Year Survivors of Childhood Cancer: The Childhood Cancer Survivor Study

- Cause of death obtained for 2,534 5-year survivors of pediatric cancer
- 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
Case Example

• 35 yo male treated for Hodgkin’s disease 18 years previously presents to cardiology with worsening SOB over a 6 month period. Prior treatment included chest XRT and 300 mg/m² of anthracyclines. Known history of progressive calcifications of the aortic valve. ECHO evaluation significant for critical aortic stenosis. Preoperative card cath reveals 3 coronary arteries with >95% occlusion. Patient is taken to surgery one week later for aortic valve replacement and 3-vessel CABG.

Learning Objective #2

Review the literature regarding cardiac disease in survivors and list currently available strategies for prevention.

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

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
• The rate of CHF is 10% in patients treated with anthracyclines
Prevention of Cardiac Disease

- Decrease cumulative anthracycline dose
- Cardioprotectants
- Modes of administration and delivery
- Targeted evaluation by ECHO
- Promotion of healthy lifestyles

Limiting Cumulative Dose

Mode of administration and Pharmaceutical Preparations

- 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

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 dextrazoxane (Zinecard)
- In numerous studies has been shown to decrease elevation of troponins during anthracycline infusion and abrogate dysfunction measured by ECHO
- Widespread use has not materialized due to concerns about decreasing overall survival and increased rates of secondary leukemia in some clinical studies
• 491 patients with standard and high-risk ALL
• Randomized to two groups
  – standard anthracycline containing therapy
  – Standard plus dexrazoxane
• Median follow-up of 5.7 years
• 5 year EFS was 82%
• Dexrazoxane had no significant impact on EFS

The low incidence of secondary acute myelogenous leukemia in children and adolescents treated with dexrazoxane for acute lymphoblastic leukemia: A report from the Dana–Farber Cancer Institute ALL Consortium

• 553 patients treated on DFCI ALL consortium trials and received dexrazoxane
• 1 secondary leukemia
• Secondary leukemia is a rare event

Screening for Cardiovascular Disease in Survivors

• Evidence-based guidelines recommend yearly ECHO evaluation for children exposed at ages <5 or if cumulative dose is >300 mg/m2
• Main assessment is ejection fraction
  ★ EF less than 50% considered worrisome
  ★ 50-55% borderline
  ★ Other imaging methods may be better
Screening Adult Survivors of Childhood Cancer for Cardiomyopathy: Comparison of Echocardiography and Cardiac Magnetic Resonance Imaging

- 108 survivors with no history of cardiotoxicity (ages 22-53)
- EF calculated from Cardiac MRI detected 14% of population with an EF less than 50%
- ECHO overestimated mean EF by 5%
- ECHO had a false negative rate of 75%
- 12 survivors had EF less than 50% by CMR, but were misclassified by ECHO as normal

Limitations in Current Screening Methods

- A large number of patients with EF measurement considered normal have significant disease
- Newer Screening methods such as Cardiac MRI or Echocardiographic strain imaging may be more sensitive

Healthy Lifestyle

- Healthy Lifestyle

Summary of Prevention

- There are numerous ongoing efforts to utilize cardioprotectants, develop preventive strategies, and improve identification of at-risk survivors
- However, a greater understanding of the underlying molecular mechanisms and clinical pathogenesis is needed to move this effort forward

Learning Objective #3

With respect to the heart, review the known cell-specific molecular events induced by the well-recognized cardiotoxic chemotherapy agents
Cell Specific Effects in Myocardium

- Myocardial tissue is composed of many cell types
  - myocytes
  - fibroblasts
  - conducting cells
  - infiltrating immune cells

Myocyte Injury Mechanisms

Injury Mechanisms in Other Cell Types

- Largely overlooked
- Our current understanding of events in the myocyte do not fully explain clinical observations
- Mechanism of myocardial injury is likely complex and involves interactions between all cell types and support structures in the heart, including extracellular matrix

Learning Objective #4

Recognize the urgent need to develop laboratory models to investigate the underlying molecular mechanisms mediating chemotherapy and radiation-induced cardiotoxicity

Need for Research

- Clinical research needed to identify patients most at risk and develop better screening methods
- Laboratory models needed to understand molecular mechanisms, identify biomarkers, and develop therapeutics

Laboratory Models

- Needed to elucidate the basic science of myocardial injury
  - must account for all cell types
  - must include the ability to study both acute injury and recovery from injury (latent period)
  - Goal should focus on the identification of biomarkers and molecular targets that will enable development of therapeutics
    - novel cardioprotectants
    - therapeutics that slow pathologic progression to cardiomyopathy and CHF
Pediatric Mouse Model for Anthracycline-induced Cardiotoxicity

A Mouse Model for Juvenile Doxorubicin-Induced Cardiac Dysfunction

Output Measurements

- Collagen deposition and fibrosis
- Function (small animal ECHO)
- Tissue acquisition from control and doxorubicin-treated animals for:
  - miRNA profiling and candidate pathway prediction
  - analysis of ECM protein and mRNA expression
- All measurements can be applied to animals during acute exposure AND recovery from treatment

Summary

- Long-term survivors of pediatric cancer patient are a growing population that faces an array of severe medical problems
- Cardiac disease is a leading cause of early mortality in this population
- Anthracyclines are clearly associated with the development of cardiomyopathy and CHF

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