Cardiotoxicities of Cancer in Childhood Cancer Survivors

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Stages in the Course of Pediatric Ventricular Dysfunction

Preventive Strategies: Progressively less effective as the number increases. 
Primary prevention is possible at number 1. 
Secondary prevention is possible at numbers 2, 3, and 4.

Treatment Strategies: Greater impact with higher numbers but longer effects with lower numbers. 
Treatment is possible at numbers 4 and 5 to reduce sequelae.

Biomarkers/Surrogate Endpoints: 
Potentially more useful with lower numbers for alteration of course with interventions. 
Potentially more useful with higher numbers for decisions about transplantation.

Lipshultz, Eur Heart J 2012
Lipshultz, et al. Prog Pediatric Cardiol 2000
New Paradigm: Successful Treatment of Cancer is Determined by the Balance Between Oncologic Efficacy and Toxicity/Late Effects as Measured by Quality of Life for a Patient and Their Family Over a Lifespan

Lipshultz et al. J Clin Oncol 1993
Event-Free Survival in Children and Adolescents with Acute Lymphoblastic Leukemia on Consecutive DFCI ALL Consortium Trials, by Decade

Vrooman, Lipshultz, Sallan, PPC, 2014
National Cancer Institute
Childhood Cancer Survivor Study (CCSS)

Common late effects and relative morbidity 30 years after childhood cancer treatment:

- Neurocognitive (severe cognitive dysfunction, RR* = 10.5)
- Psychological (depression, post-traumatic stress)
- Cardiopulmonary (decreased lung volume, heart dysfunction)
  (CAD, RR = 10.4; CHF, RR = 15.1; cerebrovascular accident, RR = 9.3)
- Endocrine (growth and fertility; ovarian failure, RR = 3.5)
- Musculoskeletal (major joint replacement, RR = 54.0)
- Second malignancies (RR = 14.8)

*RR = Relative risk of survivors vs. sibling controls

Institute of Medicine, American Cancer Society
Oeffinger et al., NEJM 2006
NCI CCSS: Global risk of premature symptomatic cardiovascular disease is elevated in childhood cancer survivors.

Prevalence of Cardiovascular Risk Factors in 10,724 5-year Survivors and 3159 Siblings

- **Hypertension**
  - Survivor (40%)
  - Sibling (26%)
  - \( P < .001 \)

- **Dyslipidemia**
  - Survivor (23%)
  - Sibling (14%)
  - \( P < .008 \)

- **Diabetes**
  - Survivor (9%)
  - Sibling (6%)
  - \( P \) not sig.

- **Obesity**
  - Survivor (25%)
  - Sibling (31%)
  - \( P < .02 \)

Armstrong et al. JCO 2013
NCI CCSS: Age-Specific Cumulative Incidence of Four Major Cardiac Outcomes in 10,724 5-year Survivors Compared to 3159 Siblings

Coronary Artery Disease

Valvular Disease

Arrhythmia

Heart Failure

Armstrong et al. JCO 2013
Estimates of (A) cumulative cardiovascular and (B) cardiac mortality in the French-British CCSS (86,453 pt-yrs follow up) in the general population in France and Great Britain.
Left Ventricular Contractility (Health of Heart Muscle Cells) Progressively Worsens Over Time

Long-term follow-up is essential to see if an early doxorubicin “Hit” results in late cardiotoxicity associated with progressive cardiovascular morbidity and mortality

- >12 million US cancer survivors
- >50% anthracycline exposed

20-year Survivors
- >8-fold increased CV mortality
- >4-fold increased sudden death
- 10-fold increased atherosclerosis
- 5-fold increased myocardial infarction
- ↑ CV mortality from 15 to 25 yrs after Dox

30-year Survivors
- >3-fold increased anthracycline–associated CV mortality
- 15-fold higher rates of heart failure
- 10-fold higher rate of other CV disease
- 9-fold higher rate of stroke

Green & red lines are the upper and lower 95% CI from the predicted mean +/- 2 SE of the mean.
Cardiotoxicity 8-Years After Anthracycline Treatment of Childhood Cancer

Arrows indicate independent predictors in multivariable analyses.

Lipshultz, Colan, Sallan et al. NEJM 1995
Gender Difference

Probability of late decreased contractility 8 years after childhood cancer

Lipshultz, Colan, Sallan et al., NEJM 1995
Hearts too small for body size after doxorubicin for childhood ALL: Grinch Syndrome

DFCI Childhood ALL Cohort

- Progressive DOX cardiotoxicity transitions from an early subclinical dilated cardiomyopathy to a potentially restrictive cardiomyopathy detectable by 15+ years after exposure.

- The restrictive phase manifests as a relative decrease in LV dimension with a geometrically consequent rise in wall thickness leading to a normal thickness-dimension ratio at latest follow up.

- There is also a progressive fall in LV mass and cavity size that becomes inadequate for body size.

- Cardiomyopathy marked by shrinking myocardial and cavity size (Grinch Syndrome) appears to be a long term risk in this population.

Lipshultz, et al., ASCO 2014
Dilated Cardiomyopathy with Higher Doxorubicin Dose: NCI DFCI ALL Study

LV Fractional Shortening

LV End Diastolic Dimension

CCSS: CHF Risk Increases with Anthracycline Dose

Netherlands: CHF Risk Increases Over Time
NCI DFCI: Effect of enalapril in delaying progression of depressed LVFS in long-term survivors of childhood cancer – 6-10 yrs of benefit

Lipshultz, Sallan, Colan et al., JCO 2002
NCI DFCI Protocol 91-01: Continuous Doxorubicin Infusion is not Cardioprotective

LV Fractional Shortening Adjusted for Age

- Estimated z-score
- Normal
- *p-value for diff bet treatment groups; † p<0.01 for diff bet baseline and follow-up time point

LV Posterior Wall Thickness Adjusted for BSA

- Estimated z-score
- Normal
- *p-value for diff bet treatment groups; † p<0.01 for diff bet baseline and follow-up time point

LV Mass Adjusted for BSA

- Estimated z-score
- Normal
- *p-value for diff bet treatment groups; † p<0.01 for diff bet baseline and follow-up time point

LV End-Systolic Dimension Adjusted for BSA

- Estimated z-score
- Normal
- *p-value for diff bet treatment groups; † p<0.01 for diff bet baseline and follow-up time point

Lipshultz, Colan, Sallan et al., JCO 2003
Lipshultz, Colan, Sallan et al., Pediatrics 2012
Doxorubicin disrupts the normal catalytic cycle of topoisomerase 2 beta, causing DNA double-stranded breaks. It further leads to defective mitochondrial biogenesis and an increase in reactive oxygen species (ROS). Cardiomyocytes have myofibrillar disarray and vacuolization. Dexrazoxane binds to topoisomerase 2 beta to prevent anthracycline binding.
Mechanism of Doxorubicin Cardiotoxicity

Free Radicals
- Quinone-Semiquinone Recycling
- Dox-Iron Recycling
↓ Antioxidant enzymes
↓ Thiol Groups
Oxidative stress

Subcellular Changes

Cardiomyopathy
Congestive heart failure

Doxorubicin

DNA Intercalation
DNA-Topo II – Dox Complex

Impairs DNA replication

Anti-tumor Effects

Non-free radical mediated

Free Radical mediated
Dexrazoxane: An Iron Chelator

Doxorubicin (DOX) → Fe^3⁺ → DOX-Fe^3⁺ → OH⁺ → DOX-Fe^2⁺ → H₂O₂

Dexrazoxane (DEX) → Fe^3⁺ → H-DEX

Free radicals formed by Doxorubicin cause extensive damage to myocytes.

Hydrolysed Dexrazoxane (H-DEX) inhibits free radical formation, protecting myocytes.
Light micrographs showing protective effect of dexrazoxane against DOX-induced cardiac lesions. Toluidine stain, x 400. Myocardial vacuolization and myofibrillar loss are less severe in rats treated with dexrazoxane/DOX 12 mg/kg (C) and dexrazoxane/DOX 7 mg/kg (D) than in rats treated with 12 mg/kg DOX (A) or 7 mg/kg DOX (B) alone.

Herman, Lipshultz, et al., JCO 1999
First Study: NCI DFCI 9501 Cohort: Dexrazoxane Does Not Affect Event-Free Survival

8.7 year event-free survival: not significantly different

Barry, Lipshultz, et al., JCO 2008; Lipshultz, Colan, Sallan et al., Lancet Oncol 2010
NCI DFCI 9501 Cohort: Dexrazoxane Reduces Myocardial Injury

Day of doxorubicin treatment
- Doxorubicin
- Dexrazoxane/Doxorubicin

Lipshultz, Colan, Sallan et al., NEJM 2004
NCI DFCI ALL 9501 Cohort: Doxorubicin-Treated Children – Girls are Cardioprotected by Dexrazoxane

Lipshultz, et al., Lancet Oncol 2010
Ventricular Remodeling in Systolic and Diastolic Heart Failure as a Function of Time

McMurray, Pfeffer, Heart Failure Updates 2003

NCI DFCI ALL 9501 Cohort: Left Ventricular Thickness to Dimension Ratio in Doxorubicin-Treated Children; Dexrazoxane Blocks LV Remodeling

Lipshultz, Colan, Sallan et al., Lancet Oncol 2010

*p-value ≤ 0.05 vs Dexrazoxane +
Second Study: NCI COG 9404 T-ALL: Dexrazoxane is Cardioprotective 3 Years After Doxorubicin

LV Fractional Shortening

LV Wall Thickness

LV Thickness-to-Dimension Ratio (LV Remodeling)

†p-value for difference between groups
‡p-value for differences in change of mean z-scores between groups

Asselin, Lipshultz, ASCO 2012
Third Study: Dexrazoxane is Cardioprotective for Additive Cardiotoxicity
NCI COG AOST 0121

Herceptin/Dox Additive Cardiotoxicity Protected by Dexrazoxane

No Cardiomyopathy by NT-proBNP with Dexrazoxane

Both Groups Not Significantly Different from Normal

Both Groups Below the Cardiomyopathy Threshold

Kopp, Lipshultz, ASCO 2012
Ebb, Lipshultz, JCO 2012
Fourth Study: Dexrazoxane is Cardioprotective with Doxorubicin Dose Escalation: NCI COG P9754: No Fall in LVFS slope going from 450 to 600 mg/m² of Doxorubicin when Dexrazoxane is used

Both Groups Not Significantly Different from Normal
C282Y mutations were significantly associated with 8-fold increased risk of elevations in cTnT

<table>
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<th>Biomarkers</th>
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<th>95% CI</th>
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<td>H63D</td>
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<td>abnormal cTnT</td>
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<td>abnormal NT-proBNP</td>
<td>1.49</td>
<td>0.31-7.19</td>
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• OR: Odds Ratio
• Abnormal cTnT: >0.01ng/ml;
• Abnormal NT-proBNP: ≥150 pg/mL in infants younger than 1 year or ≥100 pg/mL in children aged 1 year or older
  * Adjusted for dexrazoxane

LV Characteristics by HFE Carrier 2 years after Randomization

Carriers showed more dilated left ventricles, LV dysfunction, thinner posterior wall thickness, and reduced LV mass than normal

Lipshultz, Colan, Sallan et al. Cancer 2013
Administration of dexrazoxane can attenuate Fe$^{2+}$ complex formation.

Administration of intravenous immunoglobulin therapy can reduce inflammatory cytokines.

Administration of L-carnitine can bolster mitochondrial function.

Anti-heart-failure therapies can attenuate further cardiac damage.

Doxorubicin cardiotoxicity is multifaceted and requires targeted multi-agent cardioprotection.
Conclusions

- Cardiotoxicity associated with cancer therapeutics can be pervasive, persistent, and progressive but missed clinically.
- Cardiovascular-related health burden will increase as this expanding population ages.
- Genetic, environmental, and temporal factors interact to cause toxicity and identify high risk groups for safer treatment options and targeted interventions.
- Screening for hemochromatosis gene mutations in children with newly diagnosed high-risk ALL might inform treatment decisions.
- In survivors of childhood high-risk ALL, continuous-infusion doxorubicin provided no long-term cardioprotection compared with bolus-infusion.
- Enalapril delays but does not prevent progressive survivor cardiotoxicity.
- Dexrazoxane is cardioprotective and allows safe dose escalation and the use of additive cardiotoxic therapies.
- Encourage pediatric oncology protocols for children with high-risk ALL containing doxorubicin to use dexrazoxane before doxorubicin dosing, and to do so in the setting of clinical trials.
- Tailored follow-up and therapies (multi-agent cocktails) are needed and may be unique.

“In Matters of the Heart, We’re in This Together.”