Practice Based Evidence for Treatment of Pregnancy and Anthracycline Cardiomyopathy

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I will not discuss off label use and/or investigational use in my presentation.

I have the following financial relationships to disclose:

- Funding - NHLBI, NIH, NCI/American Cancer Society
- Employee of: University of Texas MD Anderson Cancer Center
Things to Consider: WHO Death

- 17 Million-48% CV Diseases
- 7.6 Million-21%-Cancer
- Nearly 25 Million Deaths in the combined field

- 2/3 of all Cancer deaths from Low/Middle income countries
- Males-US-Prostate
- Females-Worldwide-Breast
- 60% of Worlds new cancer cases: Africa, Asia, Central & South America

WHO-Projections-2008
Common Cancers Treated with Anthracyclines

- Anthracycline-Based Therapies are still part of treatment in > 50% of all childhood Malignancies
- Mantle Radiation is also Standard of Care
- Early and late Presentation (Day 1-20 Years)
- Sarcoma
- Rhabdomyosarcoma
- Lymphoma
- Leukemia
- Osteosarcoma
- Wilms Tumor
- Breast Cancer (FAC)
The Initial “Pre-Chemo Consult”

- Patients from age 16 are referred by oncologist to cardiomyopathy service for risk assessment of Anthracycline-based treatment and plan

- Assessment includes H & P, screening 3D Echocardiogram (Class I) (Strain/BNP/ Troponin are MDACC protocol)

- Discussion of Risk of Cardiomyopathy (8-16%) up to 20 years after exposure

- Chemotherapy can lead to infertility/ Fertility Planning

- Risk of Left Ventricular Dysfunction prior, during and after pregnancy with prior Anthracycline-based therapy
Late Mortality Among 5 Year Survivors of Childhood Cancer CCSS

Fig 2. Cumulative cause-specific mortality.

Armstrong GT et al. JCO.2009;27:2328-2338

N=20,483
Cumulative Incidence at age 45: Cardiovascular Events (grade 3–5)

- **Coronary Artery Disease**
  - RT
  - No RT
  - Sibling

- **Arrhythmia**
  - RT
  - No RT
  - Sibling

- **Valvular Disease**
  - RT
  - No RT
  - Sibling

- **Heart Failure**
  - RT + Anthracycline
  - Anthracycline alone
  - RT alone
  - No RT or Anthracycline
  - Sibling

JCO Armstrong et al-2012
Differential Diagnosis
Cardiomyopathy in Cancer Patients
(Diagnosis of Exclusion)

- Stress Cardiomyopathy
- Sepsis (Cytokine Release Syndrome)
- Acute Myocarditis S/P BMT/SCT
- Transfusion Related Cardiomyopathy (MDS)
- Anthracycline
- Tyrosine Kinase Inhibitors (MultiKinase)
- Thyroid Disease
- Cardiac Amyloidosis
Anthracyclines
Doxorubicin Label

Doxorubicin Hydrochloride Injection, USP

The probability of developing impaired myocardial function based on a combined index of estimate at a dose of...
... Is From 35 Year-Old Data!

• 1979: Report by Von Hoff in *Ann Int Med*
  – Retrospectively reviewed records of 4018 patients who received doxorubicin
  – Definition of doxorubicin-induced CHF:
    • Clinical signs/symptoms of CHF believed to be secondary to doxorubicin by the clinician
  – No routine LVEF assessment!
A More Recent Look at the Data…

anthracycline trials

– Significant event:
  • Symptomatic CHF or
  • EF drop >20% or
  • EF drop >10% from normal to below LLN, or
  • EF drop >5% in patient already below LLN

Adapted from Swain et al. Cancer. 2003;97:2869-79.
Identification of the molecular basis of doxorubicin-induced cardiotoxicity

Sui Zhang¹, Xiaobing Liu²-³, Tasneem Bawa-Khalfe¹, Long-Sheng Lu², Yi Lisa Lyu⁴, Leroy F Liu⁴ & Edward TH Yeh¹,²

Doxorubicin is believed to cause dose-dependent cardiotoxicity through redox cycling and the generation of reactive oxygen species (ROS). Here we show that cardiomyocyte-specific deletion of Top2b (encoding topoisomerase-IIβ) protects cardiomyocytes from doxorubicin-induced DNA double-strand breaks and transcriptome changes that are responsible for defective mitochondrial biogenesis and ROS formation. Furthermore, cardiomyocyte-specific deletion of Top2b protects mice from the development of doxorubicin-induced progressive heart failure, suggesting that doxorubicin-induced cardiotoxicity is mediated by topoisomerase-IIβ in cardiomyocytes.
Two different Top2: $\alpha$ and $\beta$

Doxorubicin poisons both Top2$\alpha$ and Top2$\beta$.

Proliferating cells express Top2$\alpha$.

However, the adult heart only expresses Top2$\beta$.

New Hypothesis

Doxorubicin-induced cardiotoxicity is mediated by Top2$\beta$. 
Top2β deletion prevents doxorubicin-cardiotoxicity
Doxorubicin-induced mitochondrial change is Top2β-dependent
Zinecard®
(DEXRAZOXOXANE FOR INJECTION)

- Dexrazoxane (DZR)
- ADR-529
- ICRF 187
- NSC 169780
Incidence of CHF in Patients Receiving 300 mg/m² of DOX Before Zinecard Use With FAC (Studies 001 and 006)

![Bar chart showing incidence of CHF](chart)

- Zinecard (n = 102): 3%
- PLA (historical control) (n = 99): 22%

*P < .001*

Historical control compared groups entered sequentially into the studies and are not comparisons of prospectively randomized patients.
Comparison of LVEF at Baseline and After Chemotherapy

Data expressed as mean values. Kalay et al. JACC. Dec 2006. 48:2258-62
Overcome Trial

**Intervention Group**
- Baseline: 63.3 ± 1.3%
- 6 months: 62.9 ± 1.4%

**Control Group**
- Baseline: 64.6 ± 1.2%
- 6 months: 57.9 ± 2.8%

*N=90*
## Table 4. Clinical endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Enalapril + Carvedilol</th>
<th>Control</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Premature end of the study, n (%)</td>
<td>3 (6.7)</td>
<td>11 (24.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Total mortality, n (%)</td>
<td>3 (6.7)</td>
<td>8 (17.8)</td>
<td>0.11</td>
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<tr>
<td>Death or heart failure, n (%)</td>
<td>3 (6.7)</td>
<td>10 (22.2)</td>
<td>0.036</td>
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<tr>
<td>Death, heart failure or final LVEF&lt;45%, n (%)</td>
<td>3 (6.7)</td>
<td>11 (24.4)</td>
<td>0.02</td>
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<td>≥10% decrease in LVEF with a final LVEF&lt;50%, n (%)</td>
<td>2 (4.8)</td>
<td>2 (5.4)</td>
<td>0.9</td>
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<tr>
<td>Heart failure or ≥10% decrease in LVEF, n (%)</td>
<td>4 (9.5)</td>
<td>7 (19)</td>
<td>0.22</td>
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<td>Severe adverse events*, n (%)</td>
<td>9 (20)</td>
<td>15 (33)</td>
<td>0.15</td>
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*defined as a serious adverse event that resulted in death or was life-threatening.

**N=90**
Limited Time to Start Therapy

Figure 1: Percentage of Responders According to the Time Elapsed From AC Administration and Start of HF Therapy

AC = anthracyclines; HF = heart failure.
MD Anderson Experience with Anthracycline and Pregnancy

- Retrospective review of 337 patients
- Pregnant and exposed to Anthracycline therapy with or without Chest Radiation
- Minimum 10 years follow up (median 20)
- Control group 80 women w/o Pregnancy, however similar Anthracycline/Radiation
- Control group- 12 (15%) LVEF<50%
- Pregnancy group 17 (29%) LVEF<50%

JACC-2017, Thompson et al
MD Anderson Experience with Anthracycline and Pregnancy

- 17 (29%) had LVEF <50%
- 3 - Prior to pregnancy
- 9 - During pregnancy
- 47% recovered
- 41% Unrecovered
- 2 (11.8% died)
- Older age time of cancer Dx, had 14% Risk reduction
- Long time to pregnancy showed increased risk
- High Dose Anthracycline showed increased risk

- Pregnancy associated with 2.35 fold increase in LVSD
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<th>TABLE 1 Characteristics of Overall Population</th>
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<td>Among Pregnant Women (N = 58)</td>
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Survival of Patients with and without Recovery of LV Function
Neurohormonal Activation in Cancer Biology

Growth of Tumor

↑ Angiotensin II  👆 Norepinephrine

Angiogenesis, Proliferation, Cell Growth, Undifferentiation

Metastasis, Morbidity and Mortality
Binding to specific adrenergic receptors, β-blockers inhibit cancer cell migration and metastasis, suggesting a novel targeted therapeutic application in protecting against breast cancer disease progression.
Fig 1. (A) Relapse-free survival (RFS) and (B) overall survival (OS) in patients with triple-negative breast cancer. (C) RFS and (D) OS in patients with estrogen receptor–positive breast cancer.
Baseline Hypertensive BC Patients Treated with Beta Blockers Live Longer

Figure 1a: Hypertensive BC patients therapeutically treated with beta-blockers showed significantly (p=0.022) longer times before acquiring metastases compared to non-treated patients.

Figure 1b. Hypertensive BC patients receiving beta-blocker therapy showed significantly (p=0.011) improved 10 year survival rates compared to non-treated patients.
Conclusions

- Organizations
  - Conquer- MD Anderson Cancer Center-2001
  - Cardiology Oncology Partnership Vanderbilt USA-2004
  - International Society for Cardioncology Milan, Italy 2009
  - Brazilian Cardiology Oncology 2009 Sao Paulo, Brazil
  - Canadian Cardioncology 2010 Pan Asia Cardioncology Society-2017
Conclusions

- Little data exist in pregnant and non pregnant population, need to work within organizations for prospective database.

- Beta blockers should be considered prior, during and well after pregnancy.

- Patients should be managed as high risk and have frequent H & P.

- Unfortunately, no consensus on when and how frequent LV function should be assessed.
Thank you!

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jdurand@mdanderson.org
COG Guidelines for Cardiac Screening

- Detailed history yearly
- EKG for evaluation of QT interval at baseline
- ECHO or MUGA for evaluation of systolic function at baseline, then periodically.