Cancer Therapy Monitoring and Treatment Planning:

What Should We Be Doing to Minimize Cardiotoxic Risk?

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City of Hope Comprehensive Cancer Center
What are the Priorities in the Cardiovascular Care of Oncology Patients?

Prior to Cancer Therapy
Identify high CV risk patients; Mitigate CTX risk; Inform cancer treatment

During Cancer Therapy
Monitoring to identify CTX; Avoid dose interruptions; Prevent CV events

After Cancer Therapy
Survivorship; Decrease risk of late CV events; Improve long-term health

Need to improve upon CV screening methods and develop strategies to identify high risk patients
Why is Risk Stratification Important?

- Cardiovascular toxicity leads to dose interruptions and discontinuation of necessary cancer therapy
- Combination therapies are associated with increased cardiotoxicity; many newer agents in development
- Early identification of cardiotoxicity and institution of medications may increase likelihood of recovery
- A growing population of survivors are at an increased risk of long-term cardiovascular morbidity and mortality
Since the 1990s:
Mortality Down, Survivorship Up

In the United States...

Multiple Myeloma

5y: 22% vs. 16%, p<0.01
IRR*: 1.7 (1.3-2.2)

NHL

5y: 18% vs. 13%, p<0.01
IRR*: 1.4 (1.1-1.8)

Breast

5y: 12% vs. 10%, p<0.01
IRR*: 1.2 (1.2-1.3)

Kidney

5y: 17% vs. 12%, p<0.01
IRR*: 1.2 (1.1-1.5)

*Adjusted for: Age, sex, race/ethnicity, CVRFs

Risk of all cause mortality: *IRR=1.65, p<0.01
*Adjusted for: Age, sex, race/ethnicity, CVRFs, cancer stage

Early Institution of Cardiac Medications Increases Likelihood of LVEF Recovery

Cardiac event-free rate according to “response”

Responders according to time between cardiac diagnosis and HF meds

Partial recovery defined as LVEF increase >10% but <50%; Full recovery LVEF >50%

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Primary screening and prevention


- **Cancer diagnosis**
- **Start of treatment**
- **End of treatment**

**Recommendation 2.1**
Avoid or minimize the use of potentially cardiotoxic therapies if established alternatives exist that would not compromise cancer-specific outcomes.
*(Consensus-based; Benefits outweigh harms; Strength of Recommendation: Strong).*

**Recommendation 2.2**
Comprehensive assessment in cancer patients that includes an H&P, screening for cardiovascular disease risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking), and an echocardiogram prior to initiation of potentially cardiotoxic therapies.
*(Evidence and consensus-based; Benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong)*
At Increased Risk for Cardiac Dysfunction

• High dose anthracycline (e.g. ≥250 mg/m$^2$ doxorubicin, ≥600 mg/m$^2$ epirubicin)
• High dose (≥30 Gy) radiotherapy where the heart is in the treatment field
• Lower dose anthracycline (e.g. <250 mg/m$^2$ doxorubicin) in combination with lower dose radiotherapy (<30 Gy) where the heart is in the treatment field
• Treatment with lower dose anthracycline (e.g. <250 mg/m$^2$ doxorubicin) or trastuzumab alone, and presence of any of the following risk factors:
  – Multiple (≥2) CV risk factors: smoking, hypertension, diabetes, dyslipidemia, obesity
  – Older (≥60 years) age at cancer treatment
  – Compromised cardiac function (e.g. borderline low LVEF [50-55%), history of myocardial infarction, ≥moderate valvular heart disease)
• Treatment with lower dose anthracycline (e.g. <250 mg/m$^2$ doxorubicin) followed by trastuzumab (sequential therapy)

_J Clin Oncol_. 2017 Mar 10;35(8):893-911
45% of cases with CHF exposed to <250 mg/m²

J Clin Oncol, 2008, 26: 5537-43
Risk Profile: Therapy-Related HF

For a given exposure, there is marked variation in prevalence and severity of heart failure that is not explained exclusively by clinical risk factors.

Clinical risk factors
- Age at exposure
- Female gender
- Anthracycline dose
- Comorbidities

Genetic risk factors
- Drug metabolism and Transport
- Generation of reactive oxygen species
- Anti-oxidant defense
- DNA repair pathways
- Renin-angiotensin system

Therapy-Related Heart Failure
Anthracycline

Prescribed dose

Internal dose

Dox-quinone

NQO1

ROS

Dox-semiquinone*

NAD(P)H oxidase multi-enzyme complex

Dox-ol

Aconitase/IRP1

Loss of Fe

Homeostasis

SOD2, APOE

ABCC1, ABCC2

CBR1, CBR3

HFE

NAD(P)+

NAD(P)H

Energy/Redox

Impairment

Myocyte apoptosis

Maladaptive LV Remodeling

Asymptomatic ↓LVEF/FS

Heart Failure

2013 Oct;163(2):205-13

<table>
<thead>
<tr>
<th>Trait</th>
<th>OR</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Female</td>
<td>2.9</td>
<td>1.4-6.0</td>
</tr>
<tr>
<td>Chest XRT</td>
<td>4.7</td>
<td>1.0-16.5</td>
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<tr>
<td>HFE (rs1799945), GC/GG</td>
<td>2.5</td>
<td>1.0-6.3</td>
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<tr>
<td>RAC2 (rs13058338), TA/AA</td>
<td>2.8</td>
<td>1.4-5.6</td>
</tr>
<tr>
<td>ABCC2 (rs818710), GA/AA</td>
<td>4.3</td>
<td>1.5-12.5</td>
</tr>
</tbody>
</table>
Receiver operating characteristic (ROC) curves

<table>
<thead>
<tr>
<th>Group</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNPs and Clinical</td>
<td>0.79</td>
<td>0.75-0.83</td>
</tr>
<tr>
<td>SNPs only</td>
<td>0.67</td>
<td>0.60-0.74</td>
</tr>
<tr>
<td>Clinical only</td>
<td>0.69</td>
<td>0.63-0.75</td>
</tr>
</tbody>
</table>

Br J Haemtol. 2013; 163:205
Among non-Hispanic whites

Evidence of gene environment (anthracycline) interaction

SNP rs1786814 (p value=1.14e-5) on gene CELF4

rs1786814*anthracycline, p=1.14x10^{-05}
Genome-wide Association Study

Germline genomics and risk prediction
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Biomarkers in Cardio-Oncology

• Existent CV biomarkers

• Multiple biomarkers
  – Determining the utility of a multi-marker approach

• New biomarker discovery
  – Discovering and validating newer mechanistic biomarkers
TnI as a Marker of Cardiac Dysfunction with High Dose Chemotherapy

- Frequent measures of TnI with each chemotherapy
  - 703 patients with TnI measured early (0, after, 12, 24, 36, 72 hrs) and late (1mo)
  - Patients divided into 3 groups based upon positivity/timing (highest TnI)

<table>
<thead>
<tr>
<th></th>
<th>TnI -/- (n=495)</th>
<th>TnI +/- (n=145)</th>
<th>TnI +/+ (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>5 (1%)</td>
<td>53 (37%)</td>
<td>53 (84%)</td>
</tr>
</tbody>
</table>

PPV 84% and NPV 99%

TnI as a Marker to Guide Therapy

- TnI measured at 6 timepoints with each chemotherapy cycle
- 114 of 473 (24%) patients showed TnI > 0.07 ng/ml
- After completion of chemotherapy, 56 TnI+ patients randomly assigned to ACE-I; 58 TnI+ to no treatment (control)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>LVEF at 3 months (%)</th>
<th>LVEF at 6 months (%)</th>
<th>LVEF at 12 months (%)</th>
<th>Cardiac events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=58)</td>
<td>61.8 ± 4.3</td>
<td>54.2 ± 8.1</td>
<td>51.9 ± 7.9</td>
<td>48.3 ± 9.3</td>
<td>31</td>
</tr>
<tr>
<td>ACE-I (n=56)</td>
<td>61.1 ± 3.2</td>
<td>61.9 ± 3.3</td>
<td>61.6 ± 3.9</td>
<td>62.4 ± 3.5</td>
<td>1</td>
</tr>
</tbody>
</table>

Role of Tn and NT-proBNP with Trastuzumab

- 452 patients from HERA study were evaluable

- Elevations in cardiac Tn (standard and hs platforms) observed
  - Primarily post anthracyclines (~13%, ~24%); smaller number with first elevations during trastuzumab (~1%, 6%)

- High variability in NT-proBNP observed

- Post-anthracycline Tn and NT-proBNP associated with first significant LVEF decline
  - Effect sizes for Tn (HR 2-4) >> NT-proBNP (HR 1.03)
  - Poor discriminative ability

Role of TnT and NT-proBNP in Pediatrics

- Children with high risk ALL treated with doxorubicin alone (n=75) or with dexrazoxane (n=81)
- Greater percentage of elevations in TnT and NT-proBNP in doxorubicin alone
- 3-month changes in TnT associated with 4-year changes in LV mass and posterior wall thickness; NT-proBNP associated with LV thickness/dimension

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Biomarkers Hypothesized to be Relevant to Doxorubicin & Trastuzumab Cardiotoxicity

- Oxidative Stress
- MPO
- Inflammation
- hsCRP
- Myocyte Injury
- High-sensitivity TnI
- Neuro-hormones
- NT-proBNP
- Fibrosis
- Galectin-3
- Inflammation/Oxid. Stress
- GDF-15
- Vascular Remodeling
- sFlt-1/PIGF

hsTnI and MPO Associated with First Cardiotoxic Event; Additive in Combination

- Biomarkers assessed at baseline and every 3 months during doxorubicin and trastuzumab
  - Patients followed for 15 months

- Baseline values not associated with cardiotoxicity

- 3 month (post-Dox) change in Troponin and myeloperoxidase significant (HR 1.34-1.38)

*Ky, et al. JACC. 2014.*
Cardiac Strain
Emerging Prognostic Index of Cardiotoxicity

Figure 3 Incremental predictive value of $\Delta e'$, $\Delta s'$, $\Delta$GLS, $\Delta$GLSR-S, and $\Delta$GLSR-E by nested logistic regression models
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Metabolomics as a discovery platform

**LV End-Systolic Wall Stress (ESWS)**

**Genome**
- DNA

**Transcriptome**
- RNA

**Proteome**
- Proteins

**Metabolome**
- Sugars, Nucleotides, AA Lipids

Metabolomic profiling
- GC-MS based platform (Metabolon; Durham, NC)
- 359 plasma metabolites; 64 pathways

Heart Failure

Phenotype
Fatty Acid (FA) Oxidation

Long-chain fatty acids major substrate for energy production in myocardium

Transport of LCFA rate limiting step in FA oxidation

Cancer Epidemiol Biomarkers Prev
2014 Jun;23(6):1109-14
Metabolomics as a discovery platform


- HR 0.78, p<0.05
- HR 3.33 p<0.05
- HR 2.70, p<0.05
- Asymmetric dimethylarginine
- N-monomethylarginine
Take Home: What is the role of biomarkers for screening *during* cancer treatment?

- Role of biomarkers as primary, solitary measures inconclusive
- **Guidelines support role as ancillary measures**
  - ESMO, ESC, COG, IGHG, ASCO
- **Change in biomarker over time may be more important than baseline levels alone**
  - In adults undergoing contemporary treatment regimen, post-doxorubicin time-point critical
  - In children undergoing ALL therapy, greatest changes observed during doxorubicin, possibly associated with late changes
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### 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>
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</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<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>Age at diagnosis, years</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>1</td>
<td>2</td>
<td>2</td>
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<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>
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<tr>
<td>Anthracycline, mg/m²</td>
<td></td>
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<tr>
<td>None</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Any</td>
<td>3</td>
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<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>
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<tr>
<td>Chest or heart RT, Gy‡</td>
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<td></td>
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<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>
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<tr>
<td>Cohort</td>
<td></td>
<td></td>
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<tr>
<td>CCSS (n = 285)$§</td>
<td></td>
<td></td>
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<tr>
<td>AUC</td>
<td>0.71</td>
<td>0.74</td>
<td>0.76</td>
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<tr>
<td>C-statistic</td>
<td>0.72</td>
<td>0.76</td>
<td>0.77</td>
</tr>
</tbody>
</table>
**COG ALTE1621:**

**HF Risk Reduction in childhood cancer survivors**

*Phase IIb randomized placebo-controlled clinical trial*

**Randomize**

- Childhood CA survivors treated with high dose anthracycline (≥250 mg/m²)
  - N= 250

**2wk run-in**

- 3.125mg/day

**If tolerating,** **escalate**

- Carvedilol 12.5mg/day total 2 yrs
  - N=125

**Placebo x 2 years**

- N=125

**NIH/NCI: R01CA196854 (Armenian)**
## CVD prevention studies in at risk survivors of childhood and young adult cancers

<table>
<thead>
<tr>
<th>Study objective</th>
<th>Population</th>
<th>Design</th>
<th>Outcome(s)</th>
<th>Status</th>
<th>Funding (PI)</th>
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</thead>
<tbody>
<tr>
<td>Determine if a web-based diet and activity intervention can achieve meaningful weight loss</td>
<td>Adult aged, obese survivors of acute lymphoblastic leukemia</td>
<td>Randomized controlled trial</td>
<td>Weight loss after 24 months</td>
<td>In follow-up</td>
<td>R01 CA18739704 (Tonorezos)</td>
</tr>
<tr>
<td>Determine if a web-based physical activity intervention can improve fitness</td>
<td>Childhood ALL patients within 3 months of completing therapy</td>
<td>Randomized controlled trial</td>
<td>Difference in the physiologic cost index 24 weeks after intervention</td>
<td>Enrolling participants</td>
<td>R01 CA193478 (Ness)</td>
</tr>
<tr>
<td>Determine if a survivorship care plan counseling intervention can improve control of cardiovascular risk conditions</td>
<td>Adult-aged survivors at high risk of premature cardiovascular disease</td>
<td>Randomized controlled trial</td>
<td>BP, cholesterol, sugar, and lipid measurements after 12 months</td>
<td>Enrolling participants</td>
<td>R01 CA193478 (Chow)</td>
</tr>
<tr>
<td>Determine if mobile intervention with tailored feedback can improve physical activity levels</td>
<td>Young adult (18-39 y) cancer survivors</td>
<td>Randomized controlled trial</td>
<td>Objectively-measured PA (ActiGraph accelerometers)</td>
<td>Enrolling participants</td>
<td>R01 CA204965 (Valle)</td>
</tr>
</tbody>
</table>
Take Home: What is needed for appropriate CVD risk stratification and risk reduction in cancer *survivors*?

- Large longitudinal studies in survivors of adult-onset cancers (e.g., breast, CRC, renal)
  - Characterize markers (blood, imaging) of chronic CV injury
  - Appropriate risk prediction models
    - Epidemiology of disease, cancer treatment exposures
- Prevention efforts that extend beyond primary, to secondary
- Cost-effectiveness studies
- Dissemination into clinical care guidelines and practice