Cardiovascular Imaging Endpoints in Oncology Clinical Trials

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Outline and Proposed Questions

• Cardio-Oncology Clinical Trial Study Design *(What areas of study design need to be addressed to detect CV signals?)*

• Imaging Tools & Data Endpoints *(Standard data fields?)*
  – Echocardiography
  – PET/CT
  – Cardiac MRI

• Role of Core Lab in Cardio-Oncology Trials *(Imaging adjudication?)*

• Future Directions in Clinical Trial Design *(Specific considerations in oncology clinical trials)*
Critical Considerations in Clinical Trial Design

• How do we develop personalized, evidence-based treatment strategies with the goal of maximal therapeutic benefit and minimal toxicities?

• How do we obtain high-quality, robust data to effectively and efficiently characterize the disease and response to treatment?

• What is the fundamental question of interest within the clinical trial? What is the CV question of interest?

• What is the potential cardiotoxic signal based upon hypothesized mechanisms and pre-clinical data?

Heart Failure with reduced or preserved ejection fraction, Valvular disease, Pulmonary hypertension, Pericardial disease

Atherosclerosis, Coronary Vasospasm, Dyslipidemia

Peripheral Arterial Disease

Hypertension

Arrhythmia/Long QT

Cancer Therapies Can Affect the CV System in Multiple Ways
Imaging Endpoint is a Function of Outcome of Interest

Echocardiography (systolic, diastolic function, hemodynamics); Cardiac MRI, catheterization

Heart Failure (preserved, reduced)/Cardiomyopathy; Pulmonary hypertension, Valvular & Pericardial disease

Cardiac CT, PET/CT, SPECT, catheterization

Coronary artery disease, microvascular disease

Ultrasound imaging, ankle brachial index

Peripheral Arterial Disease

Noninvasive BP, Arterial tonometry

Hypertension

Electrocardiogram, holter monitors

Arrhythmia
Quantitative Echocardiography Provides Detailed Phenotypic Data

<table>
<thead>
<tr>
<th>Echocardiographic Measure</th>
<th>Functional or Structural Alteration</th>
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<tbody>
<tr>
<td>2D/3D LV and RV size and mass</td>
<td>Ventricular Structure</td>
</tr>
<tr>
<td>2D/3D LV and RV Strain, Strain rate, Ejection fraction</td>
<td>Systolic Function</td>
</tr>
<tr>
<td>E/a, e’, a’, E/e’</td>
<td>Diastolic Function</td>
</tr>
<tr>
<td>Ea, E_{es}, Ea/E_{es}</td>
<td>Ventricular/Vascular Stiffness</td>
</tr>
<tr>
<td>Twist, Torsion</td>
<td>Systolic/Diastolic Deformation</td>
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<tr>
<td>Regurgitation, stenosis</td>
<td>Valvular disease</td>
</tr>
<tr>
<td>Stroke volume, cardiac output, pulmonary pressures, filling pressures</td>
<td>Hemodynamics</td>
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</table>
Noninvasive Measures of Ventricular-Arterial Strain Coupling and Circumferential Strain Predict Cancer Therapeutics–Related Cardiac Dysfunction

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Aktinyemi Bajulaye, BA,e Susan Domchee, MD,e,fc Angela DeMichele, MD, c, MSCF,g,h Amy Clark, MD, h, i
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
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<tbody>
<tr>
<td>Longitudinal strain</td>
<td>0.612</td>
</tr>
<tr>
<td>Circumferential strain</td>
<td>0.655*</td>
</tr>
<tr>
<td>Radial strain</td>
<td>0.624</td>
</tr>
<tr>
<td>Ea/Ees</td>
<td>0.703*</td>
</tr>
</tbody>
</table>

* p<0.05
Most pronounced changes in function with doxorubicin & trastuzumab
- Modest, but sustained changes with doxorubicin

Correlates of declines (and recovery) in cardiac function:
- Volumes, strain, and ventricular-arterial coupling (afterload); afterload also associated with worse symptoms

N = 227 participants; 1,255 echocardiograms
Maximum f/u time for subcohort = 3.5 years
Myocardial Perfusion Imaging

- Positron Emission Tomography (PET) or single-photon emission computed tomography (SPECT) radiotracers are a tool to evaluate myocardial perfusion, cardiac function, and coronary vasculature.

- Outcome measures: perfusion defects, myocardial blood flow, coronary flow reserve, calcium score, LVEF.

- Additional measures: markers of inflammation, cell death, metabolism.

Interaction of Impaired Coronary Flow Reserve and Cardiomyocyte Injury on Adverse Cardiovascular Outcomes in Patients Without Overt Coronary Artery Disease

*Circulation.* 2015;131:528-535.

Taqueti T… Di Carli M. *Circulation.* 2015.
Cardiac magnetic resonance imaging (CMR) can characterize with high reproducibility cardiac size and function (LVEF, volumes, mass, strain).

Gain unique qualitative and quantitative insight into myocardial tissue through T1/T2 mapping, extracellular volume index, and delayed enhancement.

- Edema, inflammation, fibrosis

Jordan J… Hundley WG. Circ. Img. 2016.
Core Lab Processes Designed to Ensure Robust Data Collection

- Processes start with trial design; core lab involved early and throughout trial in study design and echo analysis plan

- Institute common image acquisition protocol that is comprehensive yet feasible

- Require high data quality prior to patient enrollment (QC echocardiogram)

- Dedicated personnel training (webcasts, instructional videos, face-to-face meetings)

- Maintain data quality throughout trial duration

Core Lab Established Data Quality and Standards

- Develop **rigorous** image analysis plan
  - Personnel training plans, analysis tools, measurements, analytic plans, quality assessment tools

- Establish standard method for image transfer

- Secure environment for data storage

- Develop case report forms for data entry and secure database

- Perform regular data QA

- Perform regular QC measures to decrease variability and maximize **reproducibility** (e.g. LVEF concordance correlation coefficients = 0.94 in Penn core lab)

CV Phenotyping in Clinical Trials: Needs and Opportunities

• Critical need to create an efficient infrastructure to ask impactful questions

• Develop innovative strategies to obtain high-quality data, related to both exposures and outcomes

• NCI-funded ECOG-ACRIN Cardiotoxicity Working Group created to meet these needs:
  – Harmonization of adverse event reporting of cardiac events by CTCAE
  – Building imaging banks and biobanks of data
  – Enhanced patient education (www.cardiosmart.org)
Trials need to include careful assessment of both cancer and CV measures
- Short and long-term
- Understand the clinical impact of changes in sensitive measures of cardiac function

Cancer treatments are rapidly changing; an ongoing, collaborative dialogue between basic, translational, and clinical scientists, and oncologists and cardiologists is increasingly needed.
THANK YOU
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