Current Landscape of LV Dysfunction Monitoring: What are the Challenges and Opportunities?

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Disclosures

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Objectives

• Left Ventricular (LV) dysfunction - Definitions
• Cardiac imaging techniques
• Cancer therapeutics ~ LV dysfunction
• Current regulatory and clinical practices of LV function monitoring
• How to utilize Cardiac function Monitoring to Advance CV Safety and Improve Patient Outcomes?
LV function, LVEF and LV dysfunction

• Left ventricular (LV) systolic function ≠ LV Ejection Fraction (LVEF)
  – LVEF = One (heart beat) measure of the contractile function of the left ventricle
    • Physiologic and technique-related variability (MUGA, Echo, CMR)
  – LVEF is a key predictor of Outcomes
    • In cardiovascular cohorts
    • In patients receiving cancer therapies (anthracyclines)
  – LV dysfunction has many definitions
    • Decrease in LVEF of >10% to a value of <53% (50%)
    • Or presence of HF symptoms with LVEF decrease
Cardiac Function in Oncology Practice


CHANGES IN CLINICAL PRACTICE

- Reduce the anthracycline dose
- Check baseline LV systolic function
- Monitor LVEF (only during treatment at high doses)
- ERNA (MUGA)


Singal & Iliskovic. NEJM 1998; 339:900
LVEF Monitoring in Trastuzumab Trials

2001: Trastuzumab improves survival in metastatic HER2-positive breast cancer  
Slamon et al. NEJM. 2001;344:783

<table>
<thead>
<tr>
<th>Cardiotoxicity</th>
<th>trastuzumab + AC</th>
<th>AC</th>
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<tbody>
<tr>
<td>Cardiac dysfunction %</td>
<td>28</td>
<td>10</td>
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<tr>
<td>NYHA III/IV CHF, %</td>
<td>19</td>
<td>3</td>
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CHANGES IN THE DESIGN OF CLINICAL TRIALS OF TRASTUZUMAB IN EARLY BREAST CANCER

- Changes in administration
- Stringent CV eligibility criteria
- Cardiac monitoring schema with early stopping rules
- NEW ERA OF CARDIAC MONITORING IN ONCOLOGY TRIALS
Current Monitoring LV Dysfunction in Oncology Clinical Practice

• **Anthracyclines**
  - Pre-treatment LVEF assessment
  - Repeat LVEF assessment with higher cumulative doses
  - Avoid anthracycline in patients with LV dysfunction

• **HER2 targeted agents** (trastuzumab, pertuzumab and TDM-1)
  – Pre-treatment LVEF assessment
  – On-treatment “frequent LVEF assessment” (q 3 months)
  – Therapy held for LVEF decreases, stopped if not improved

• **Other Cancer Therapeutics including Novel Agents:**
  No routine LV assessment
Pathogenesis of heart failure

Mann D L Circulation 1999;100:999-1008
Stages of heart failure, ACC/AHA 2013

**At Risk for Heart Failure**

**Stage A**
At high risk for HF, but without structural heart disease or symptoms of HF

- e.g.: Patients with:
  - hypertension
  - atherosclerotic disease
  - diabetes
  - obesity
  - metabolic syndrome
  - Patients:
    - using cardiotoxins
    - with FHx CM

**THERAPY GOALS**
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome

**DRUGS**
- ACEI or ARB in appropriate patients for vascular disease or diabetes

**Stage B**
Structural heart disease, but without signs or symptoms of HF

- e.g.: Patients with:
  - previous MI
  - LV remodeling including LVH and low EF
  - asymptomatic valvular disease

**THERAPY GOALS**
- All measures under Stage A
- ACEI or ARB in appropriate patients
- Beta-blockers in appropriate patients

**Stage C**
Structural heart disease with prior or current symptoms of HF

- e.g.: Patients with:
  - known structural heart disease
  - shortness of breath and fatigue, reduced exercise tolerance

**THERAPY GOALS**
- All measures under Stages A and B
- Dietary salt restriction
- Diuretics for fluid retention
- ACEI
- Beta-blockers

**DRUGS FOR ROUTINE USE**
- Aldosterone antagonists
- ARBs
- Digoxin
- Hydralazine/nitrates

**DEVICES IN SELECTED PATIENTS**
- Biventricular pacing
- Implantable defibrillators

**Stage D**
Refractory HF at Rest

- e.g.: Patients who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

**THERAPY GOALS**
- Appropriate measures under Stages A, B, C
- Decision re: appropriate level of care

**OPTIONS**
- Compassionate end-of-life care/hospice
- Extraordinary measures - heart transplant - chronic inotropes - permanent mechanical support - experimental surgery or drugs

*Yancy C et al. J Am Coll Cardiol. 2013;62(16)*
Current LV Landscape of LV Dysfunction Monitoring

• **CV Risk Prediction and Outcomes**
  - **Predictors**: LV function parameters (strain), biomarkers
  - **Outcomes**: CV and Oncology outcomes, surrogate outcomes (LVEF)

• **Evidence-based Prevention and Treatment**
  - Which agent? - beta-blockers, ACE-inhibitor, statin
  - For which patient? - strategies for high risk patients

• **Long term CV safety and Outcomes**

• **Design of New Trials**
  - What are the CV parameters needed for drug approval?
Current LV Landscape of LV Dysfunction Monitoring

LVEF

Cancer Treatment

Yes

No

Outcomes

CV Risk Stratification
- CV risk factors
- Cardiac imaging parameters (LVEF, strain, diastole)
- Biomarkers

Individualized CV Intervention
- Based on cardiac risk stratification
- Based on cancer treatment plan

Improved Outcomes
- CV and Oncology outcomes
- Relevant surrogate outcomes
PRESENTATIONS
How do we include CV safety in a contemporary cancer-therapeutics trial?

Comprehensive CV assessment and follow-up

- Baseline CV risk data
- Informed choice of CV imaging modalities (Core labs)
- Biomarkers
- **Outcomes** – Strategies for prevention?
- Long term follow-up
PANEL DISCUSSION: Question 2

• What are the elements need to be collected to assure CV safety of a cancer-therapeutics prior to drug approval?

  – Can CV imaging data in clinical trials inform drug development, approval and labeling?
  – Can CV imaging impact treatment - oncology and CV treatment?
Population-based Cohort and Risk Prediction

- 12,500 women with breast cancer diagnosed between 1999-2007

PANEL DISCUSSION: Question 3

• How do we assure CV safety after the drug approval?
• Can we design post-marketing Registries to measure and improve outcomes?
  – Designed based on trial data
  – Invaluable resource for Safety Monitoring, Improved CV Risk stratification and Intervention
  – Must have Validation and Quality control systems: examples from CV world
Thank you.