Chemotherapy Cardiotoxicity: can echo help?
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No disclosures

59 year old woman
Sister diagnosed with breast cancer at age 39
Self-examination: lump in her left breast June 09

Biopsy: ER- HER2+ poorly differentiated invasive carcinoma

Treatment: tumorectomy
adriamycin every 3 weeks x 4
paclitaxel+trastuzumab every week for 12 weeks
trastuzumab for 9 more months (total 1 year)

3 months
6 months

69%
63%
49%
Cancer therapies and the heart background

- More intensive therapies, better supportive care has led to higher cancer survival rates
  - But increase in cardiovascular complications
    - More older cancer survivors
      - Both those living longer and those getting cancer at older age
        - Higher CV risks
    - Newer agents (monoclonal Ab, tyrosine kinase inhibitors, etc) have cardiac toxicities or exacerbate toxicity of older agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Short term effects</th>
<th>Long term effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Arrhythmia, Pericarditis/myocarditis</td>
<td>Reduced EF, Progressive decrease in LVEF, overt HF</td>
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<tr>
<td>Cisplatin</td>
<td>Myocardial ischemia/MI, HTN, HF, anthriniias, heart block, endocardial fibrosis</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Pericarditis/myocarditis, HF, bradycardia</td>
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<tr>
<td>Taxanes</td>
<td>Bradycardia, Ht block, arrhythmias, HF, myocardial ischemia</td>
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<tr>
<td>Fluorouracil</td>
<td>HF, ectopy, ischemia/MI</td>
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<tr>
<td>Methotrexate</td>
<td>Anthrinniias. Ischemia/MI</td>
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<tr>
<td>Radiotherapy</td>
<td>Angina, dyspnea, HF, intimal hyperplasia of cors, pericardial effusion, SCD</td>
<td>CAD, constrictioin, valvular heart ds</td>
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<tr>
<td>Tamoxifen</td>
<td>Venous thrombosis</td>
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<tr>
<td>Trastuzumab</td>
<td>LV dysfunction, HF</td>
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<tr>
<td>Bevacizumab</td>
<td>HTN, MI, LV dysfunction, venous thrombosis, stroke, HF, angina</td>
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<tr>
<td>Dasatinab</td>
<td>Pre-capillary pulmtn</td>
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LV dysfunction from therapies

- Anthracyclines
  - Known since the 70’s
    - Acute
      - Rare
        - Repol and QT, conduction abnormalities; ACS; Myocarditis/pericarditis
    - Chronic
      - Cumulative dose effect
      - Cardiomyocyte injury from oxidative stress
      - Ultrastructural effects
    - Irreversible cardiac effects?
LV dysfunction from therapies

- Trastuzumab
  - Antibody beneficial in patients that overexpress HER2 oncogene
  - Binds to human epidermal growth factor receptor2 (HER2)
  - Prevents HER2 interaction with HER4 receptor
    - Affects signaling involved in cardiomyocyte repair under stress
      - Such as oxidative stress in setting of anthracyclines
    - LV dysfunction in up to 1/3 + CHF in 2-5% of pts treated with both tx
  - does not cause ultrastructural effects
  - Effects not dose dependent and are reversible
  - Responsive to HF therapies

- Tyrosine kinase inhibitors (> 600 agents in development)
  - Cardiac toxicity due to inhibition of normal growth, repair and survival of myocytes
  - Potentiates anthracycline-induced injury

Incidence of class III/IV HF as a function of time interval between AC and trastuzumab

Ewer et al, Nat. Rev. Cardiol.2010;7:564-575

HERA Breast Cancer Trial

- 1 or 2 years of trastuzumab vs. observation after completion of (neo)adjuvant chemo
  - > 1500 pts per group
- All had normal LVEF after completing chemo (with or without radiation) prior to initiation of trastuzumab
  - 94% treated with AC
- Severe HF requiring trastuzumab withdrawal
  - 0.8%
- Significant LVEF decrease (10% to an EF < 50%)
  - 3.6%
- Trastuzumab cardiac effects reversible in most
  - Recovery from cardiac endpoint in 80%
    - If dosing stopped or delayed + LV dysfunction treated
Goal: early detection of LV dysfunction

- Modify therapy
  - Dose reductions, dosing intervals, alternate therapies
- Interventions to slow progression of LV dysfunction or prevent late toxicity
  - Beta blockers, ACE inhibitors, ARBs

Definition of cardiotoxicity varies

- Symptomatic HF or death
  - Clinical signs without LVEF criteria
- LVEF criteria in different trials
  - Cardiac Review and Evaluation Committee of trastuzumab-associated cardiotoxicity (J Clin Onc. 2002;20:1215-1221)
    - “cardiomyopathy with decreased LVEF”
    - LVEF decrease of > 5% to LVEF < 55% + symptoms of HF
    - Asymptomatic decrease in LVEF > 10% to < 55%
  - LVEF decrease to below 50% or 45%
  - LVEF decreases > 20% from baseline but remaining in normal range
  - Asymptomatic decrease in LVEF > 10% from baseline

Anthracycline-induced cardiomyopathy treatment

Cardinale et al. JACC 2010;55:213-20

- 201 pts with LVEF < 45% due to anthracycline
- Enalapril + carvedilol
- LVEF monitoring for mean of 3 years
  - 42% responders, 13% partial responders, 45% nonresponders
  - Early detection and treatment initiation important
Guidelines for monitoring chemotherapy-induced toxicity

- Available for anthracyclines in children but none for adults – serial EF or biomarker makes sense
  - ? Method, duration of f/u, frequency, threshold values
- What constitutes cardiotoxicity?
  - Varying definitions
- Challenge of LVEF measurement variability
- Biomarkers
  - Troponin
    - Used in high dose anthracyclines
    - Value in low to moderate dose AC not established

Identifying high risk patients

- Pre-treatment LVEF predictive of subsequent cardiotoxicity in breast cancer patients treated with anthracyclines or anthracyclines/trastuzumab
  - 3 yr incidence of symptomatic HF function of LVEF early after AC
    - 12.5% with LVEF 50-54%
    - 3.8% with LVEF 55-64%
    - 0.9% with LVEF > 65%

Strategies for early detection of cardiotoxicity - Improve existing indices (LVEF) with contrast agents

- ASE/EAE Guidelines ASE/EAE (Mulvagh SL, JASE 2008)
- Contrast if 2 or more endocardial segments not visualized
  - Reduced measurement variability
3-dimensional echocardiography – reduced LVEF variability

no foreshortening, no geometric assumptions

Baseline

EDV 63 ml, LVEF 60%

3 months

EDV 80 ml, LVEF 51%

3D and 2D LVEF fail to show subclinical changes detected by deformation indices

Hare JL, Am Heart J 2009

Are diastolic function parameters valuable?

• Small studies demonstrate alterations of diastolic function with AC
  – None show prognostic value or correlation between these changes and later systolic HF

• Stoddard et al, Am J Cardiol 1992;20:62-9
  – Increase in IVRT of > 37% 3 weeks post-chemo predictive of systolic dysfunction at 3 months
    • 78% sens, 88% spec

• No large studies available
  – Specificity of findings unclear

Can stress unmask subclinical dysfunction post-chemo?

• McKillop et al, Am Heart J 1983;106:1048-56
  – Stress RNA LVEF higher sens much lower spec than rest EF for development of later HF (dox)

• DSE – conflicting results

• Stress imaging not utilized routinely to monitor for cardiotoxicity
  – CPET and exercise capacity may have value
    • Exercise difficult in this patient population
In children higher cumulative doses of anthracyclines associated with smaller exercise-induced increase in LV function

Smibert E, Ped Blood Cancer 2004

Myocardial deformation imaging
strain, strain rate

- Potential to detect subtle regional abnormalities that may not impact global LV measures
  - Animal and human studies show longitudinal and radial strain changes before LVEF in AC alone or in combination with trastuzumab and taxanes
  - Correlates with early myocyte apoptosis

Neilan et al, Eur Heart J 2006;27:1868-75

Value of deformation indices

Ganame J, Am J Cardiol 2007

Acute changes strain (2D)


Acute changes (TDI)


Late changes (TDI)
Decreases in longitudinal strain at 3 months predictive of LV dysfunction at 6 months in breast ca pts receiving AC, paclitaxel and Trastuzumab

- 32% of 81 pts - CREC defined cardiotoxicity
- No pre-treatment differences (including LVEF)
- Reversible in 80% of those with cardiotox

Peak longitudinal strain < -19% at completion of AC predictive
hs-Trop > 30 pg/ml at AC completion also predictive of later cardiotoxicity
LVEF, diastolic function at AC completion not predictive

91% neg PV when long strain reduced or hs-trop < 30 pg/ml


Predicting trastuzumab cardiotoxicity
Fallah-Rad et al, JACC 2011;57:2263-70

- Lateral s’ identified all who subsequently develop cardiotoxicity
  - Serial cMR showed later development of LGE in lateral wall

<table>
<thead>
<tr>
<th>Echocardiographic Variables</th>
<th>Cutoff Values</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF %</td>
<td>50</td>
<td>0.95 (0.89-0.96)</td>
<td>0.80</td>
<td>0.96</td>
<td>0.68</td>
</tr>
<tr>
<td>Longitudinal strain</td>
<td>2.00</td>
<td>0.70 (0.61-0.80)</td>
<td>0.82</td>
<td>0.60</td>
<td>0.62</td>
</tr>
<tr>
<td>Tissue strain</td>
<td>0.80</td>
<td>0.80 (0.77-0.90)</td>
<td>0.81</td>
<td>0.60</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Early Detection of Chemo-related Cardiotoxicity
Trastuzumab After Anthracyclines for Breast Ca

Adapted from Fallah-Rad et al, JACC 2011;57:2263 by J Lindner MD
57 yo F with metastatic breast CA
tristuzumab, carboplatin, bevacizumab
LVEF decrease to 46%
What to do with trastuzumab?

Cardiotoxicity and Chemotherapy

- Identify populations at risk for cardiac side effects
  - Treatment regimens
  - Patient co-morbidities
- Early detection of subclinical LV dysfunction
  - Potential prognostic value (requires validation)
  - More frequent monitoring (combine with biomarkers)
- Identifying overt decreases in LVEF
  - Dose adjustments
  - Change in dosing interval
  - Change in therapy
  - Heart failure treated like any other heart failure
- Long term consequences in survivors?