Breast Cancer: CV and Oncologic Treatment Planning from Simple to Complex

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Disclosures

• Karen Smith: Pfizer (research grant), Abbot (family member stock), Abbvie (family member stock)

• Jennifer Liu: None
Objectives

– Understand contemporary breast cancer treatment paradigms

– Discuss potential cardiovascular toxicity associated with breast cancer treatment

– Identify and manage cardiovascular risk in breast cancer patients before, during and after systemic therapy for breast cancer

– Understand the importance of the cardio-oncology team approach in breast cancer
Case #1

- 65 yo female who presented with a left breast lump.
- Breast imaging revealed a 1.5 cm mass in the left breast. The axilla was negative clinically.
- Biopsy of the breast mass showed grade 3 invasive ductal carcinoma, ER negative, PR negative, HER2 positive.
- She underwent left lumpectomy and left axillary sentinel node biopsy revealing a 2 cm tumor in the breast and 1 of 4 involved lymph nodes (T2N1M0, Stage IIB).
- Scans showed no evidence of distant metastatic disease.
- Referred to medical oncology by her surgeon for adjuvant systemic therapy which will be followed by radiation.
Case #1 continued

- PMH: obesity, HTN, DM, diet-controlled hyperlipidemia. No known heart disease
- Meds: metformin, HCTZ
- SH: sedentary, non-smoker
Approaches to Treating Early Breast Cancer

**Adjuvant Approach:**

1. Surgery → Adjuvant Systemic Therapy +/- Radiation

**Considerations in selecting adjuvant approach:**
- Goal of therapy: reduce risk of recurrence
- Consider for: small tumors, operable, breast conservation candidate, clinically negative axilla, subtypes unlikely to respond to neoadjuvant therapy, subtypes for which extent of residual disease not strongly associated with long term outcomes

**Neoadjuvant Approach:**

1. Neoadjuvant Systemic Therapy → Surgery → Adjuvant Systemic Therapy +/- Radiation

**Considerations in selecting neoadjuvant approach:**
- Goal of therapy: shrink tumor prior to surgery, reduce risk of recurrence
- Consider for: inoperable or not breast conservation candidate at diagnosis, bulky axillary involvement, subtypes likely to respond to neoadjuvant therapy, subtypes for which extent of residual disease strongly associated with long term outcomes (e.g. TN, HER2+)
Breast Cancer Subtypes

Markers:
- Estrogen Receptor
- Progesterone Receptor
- HER2

- Hormone receptor positive, HER2 negative
- Triple negative
- Hormone receptor positive, HER2 positive
- Hormone receptor negative, HER2 positive
HER2-Positive Breast Cancer

• ~20% of breast cancers HER2-positive
• HER2-positivity defined by:
  a) HER2 protein over-expression (assessed by immunohistochemistry) or
  b) gene amplification (based on HER2 copy number or HER2:CEP17 ratio on
      in situ hybridization)
• Historically, HER2 positive breast cancers more aggressive, characterized by poor prognosis
• HER2-positivity predicts response to HER2-targeted therapies
• Favorable prognosis in modern era with HER2-targeted therapies

Slamon Science 1987;235(4785):177–182
Wolff J Clin Oncol 36:2105-2122, 2018
Audience Response Question #1

Which adjuvant regimen would you consider for this case with T2N1 HER2-positive breast cancer?

A. Paclitaxel/trastuzumab (TH)
B. Docetaxel/Carboplatin/Trastuzumab (TCH)
C. Docetaxel/Carboplatin/Trastuzumab/Pertuzumab (TCH/P)
D. Doxorubicin/Cyclophosphamide (AC) → Paclitaxel/Trastuzumab/Pertuzumab (TH/P)
E. C or D
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E. C or D
Commonly Used Breast Cancer Drugs with Potential CV Effects

• Anthracyclines (e.g. doxorubicin, epirubicin)
• HER2-targeted therapies (e.g. trastuzumab, pertuzumab, ado-trastuzumab emtansine)
Doxorubicin

- An anthracycline
- Mechanism: inhibit topoisomerase II, form oxygen free radicals that cause DNA breaks
- Anthracyclines are used to treat multiple types of cancer: e.g. breast cancer, leukemia, multiple myeloma, gastric cancer, ovarian cancer
- Common backbone for many breast cancer regimens: AC (doxorubicin/cyclophosphamide)
Trastuzumab

- Humanized monoclonal antibody against HER2
- Binds to extra-cellular domain 4 of HER2 → prevents its homo- and hetero-dimerization
- HER2-positivity predicts response to trastuzumab
- Mechanisms of action include:
  - Activates antibody dependent cellular cytotoxicity
  - Inhibits downstream intracellular signaling
  - Inhibits angiogenesis
  - Inhibits cleavage of the extra-cellular domain
  - Increases intracellular HER2 degradation

Singh British Journal of Cancer (2014)111:1888-1898
O’Sullivan Current Breast Cancer Reports (2014);6(3):169-182
Major Adjuvant Trastuzumab Trials for Breast Cancer

General design for adjuvant trastuzumab trials:
Chemo vs chemo/trastuzumab

Primary endpoint: disease free survival

# Key Adjuvant Trastuzumab Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>Median F/u</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B31</strong></td>
<td>AC→T</td>
<td>8.4 years</td>
<td>62.2% 10 year DFS</td>
<td>75.2% 10 year OS</td>
</tr>
<tr>
<td></td>
<td>AC→TH→H (1 yr total)</td>
<td></td>
<td>73.7% 10 year DFS</td>
<td>84% 10 year OS</td>
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<td>79% 10 year OS</td>
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<td>Chemo → H (2 yrs)</td>
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<td>69% 10 year DFS</td>
<td>80% 10 year OS</td>
</tr>
<tr>
<td><strong>BCIRG 006</strong></td>
<td>AC→D</td>
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<td>(Slamon N</td>
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<td>92% 5 year OS</td>
</tr>
<tr>
<td>Engl J Med</td>
<td>TCH→H (1 yr total)</td>
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<td>81% 5 year DFS</td>
<td>91% 5 year OS</td>
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**Combined Analysis**:
- Concurrent chemotherapy + HER2 targeted therapy → completion of 1 year total of HER2 targeted therapy

**Standard approach**:
- Concurrent chemotherapy + HER2 targeted therapy → completion of 1 year total of HER2 targeted therapy

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**Key Points**
- Median follow-up for B31 and 9831 trials is 8.4 years.
- HERA trial has follow-ups for 1 year and 2 years.
- BCIRG 006 trial has follow-ups for 5 years.

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**Notes**
- DFS: Disease-free survival
- OS: Overall survival
- AC: Anthracycline-based chemotherapy
- T: Taxane
- TH: Trastuzumab
- H: Herceptin
- DH: DH: Trastuzumab followed by Herceptin
- Chemo: Chemotherapy
Reducing Therapy for Low-Risk HER2-Positive Early Breast Cancer

- APT trial:
  - Single arm
  - < 3 cm tumors
  - Adjuvant Paclitaxel/Trastuzumab weekly x 12 → Trastuzumab (1 year total)
  - 3 year DFS: 98.7%
Pertuzumab

- Humanized monoclonal antibody against HER2
- Binds to extra-cellular domain 2 of HER2 → prevents HER2:HER3 hetero-dimerization → inhibits downstream signaling
- Activates antibody dependent cellular cytotoxicity
- Minimal activity as a single agent → synergistic when used in combination with trastuzumab
## Pertuzumab in the Neoadjuvant Setting

### Neosphere Trial (Gianni Lancet Oncol 2012):

<table>
<thead>
<tr>
<th>N=417</th>
<th>Docetaxel + trastuzumab</th>
<th>Docetaxel + trastuzumab + pertuzumab</th>
<th>Pertuzumab + trastuzumab</th>
<th>Docetaxel + pertuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pCR</strong></td>
<td>29%</td>
<td>45.8%</td>
<td>16.8%</td>
<td>24%</td>
</tr>
</tbody>
</table>

### Tryphaena Trial (Schneeweiss Ann Onc 2013):

<table>
<thead>
<tr>
<th>N=225</th>
<th>FEC+ trastuzumab + pertuzumab → docetaxel + trastuzumab + pertuzumab</th>
<th>FEC→ docetaxel + trastuzumab + pertuzumab</th>
<th>Docetaxel + carboplatin + trastuzumab + pertuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pCR</strong></td>
<td>61.6%</td>
<td>57.3%</td>
<td>66.2%</td>
</tr>
</tbody>
</table>

*High pCR rates with addition of pertuzumab to tras/chemo

*Concurrent anthracycline with pert/trast not associated with higher pCR
Adjuvant Pertuzumab

APHINITY: Trial Design

Central confirmation of HER2 status (N = 4805)

Randomisation and treatment within 8 weeks of surgery

Chemotherapy* + trastuzumab + pertuzumab

Chemotherapy* + trastuzumab + placebo

Anti-HER2 therapy for a total of 1 year (52 weeks) (concurrent with start of taxane)

Radiotherapy and/or endocrine therapy may be started at the end of adjuvant chemotherapy

Note: ~75% received an anthracycline-containing chemo regimen in both arms

*A number of standard anthracycline-taxane-sequences or a non-anthracycline (TCH) regimen were allowed
Adjuvant Pertuzumab

APHINITY TRIAL RESULTS:
*Statistically significant improvement in invasive DFS with addition of pertuzumab. But, absolute benefit small. Greatest benefit in node positive.

Returning to Case #1...

Which adjuvant regimen would you consider for this case with T2N1 HER2-positive breast cancer?

A. Paclitaxel/trastuzumab (TH)
B. Docetaxel/Carboplatin/Trastuzumab (TCH)
C. Docetaxel/Carboplatin/Trastuzumab/Pertuzumab (TCH/P)
D. Doxorubicin/Cyclophosphamide (AC) → Paclitaxel/Trastuzumab/Pertuzumab (TH/P)
E. C or D

*Recommend a regimen including trastuzumab and pertuzumab. AC→TH/P or TCH/P are options. You select AC→TH/P.
Case #1: The selected cancer treatment approach

- **Left lumpectomy and left axillary sentinel node biopsy**
- **AC q 2 weeks x 4**
- **Weekly paclitaxel x 12 with concurrent trastuzumab/pertuzumab every 3 weeks x 4**
- **Radiation to L breast and regional nodes x 3 weeks**
- **Trastuzumab/pertuzumab every 3 weeks x 13**
Case #1: The selected cancer treatment approach

- Left lumpectomy and left axillary sentinel node biopsy
- AC q 2 weeks x 4
- Weekly paclitaxel x 12 with concurrent trastuzumab/pertuzumab every 3 weeks x 4
- Radiation to L breast and regional nodes x 3 weeks
- Trastuzumab/pertuzumab every 3 weeks x 13

Baseline EF 64%
Case #1: My concerns as the treating oncologist...

- What are her cardiovascular risks?
- How should we assess her cardiovascular status at baseline?
- What can we do to reduce her cardiovascular risks?
- How should we monitor her cardiovascular status during therapy?

Referral to cardio-oncology before treatment due to CV risk factors and planned regimen with potential cardiovascular toxicity.
What factors are associated with increased cardiac risk in patients receiving trastuzumab?

A. Anthracycline exposure
B. CV risk factors (HTN, DM, atrial fibrillation, renal disease)
C. Older age
D. EF <55%
E. All of the above
Audience Response Question #2

What factors are associated with increased cardiac risk in patients receiving trastuzumab?

A. Anthracycline exposure
B. CV risk factors (HTN, DM, atrial fibrillation, renal disease)
C. Older age
D. EF <55%
E. All of the above
A Wonder Drug's Frightening Side Effect

One woman thrived on Herceptin for years – and then her heart began to fail.

By Steve Sternberg | Staff Writer  Oct. 20, 2015, at 12:01 a.m.
Scope of the Problem: Cardiotoxicity of Anthracycline/Trastuzumab During Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Rx</th>
<th>Asx LVEF ↓: &gt; 10% to &lt; 50% or LLN; or &gt; 16%</th>
<th>Class III-IV Heart Failure</th>
<th>Trastuzumab Discontinuation-Cardiac causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA¹</td>
<td>Chemo → H x 1 yr 94% rec'd anthracycline</td>
<td>4.1%</td>
<td>0.8%</td>
<td>5.1%</td>
</tr>
<tr>
<td>B-31²</td>
<td>AC → T AC → TH → H</td>
<td>Not reported 14%</td>
<td>0.8%</td>
<td>4.1%</td>
</tr>
<tr>
<td>N 9831³</td>
<td>AC → T AC → TH → H</td>
<td>4% - 5.1%</td>
<td>0.3%</td>
<td>NA</td>
</tr>
<tr>
<td>BCIRG 006⁴</td>
<td>AC → D AC → DH → H</td>
<td>11.2%</td>
<td>0.7%</td>
<td>NA</td>
</tr>
</tbody>
</table>

A=doxorubicin, C=cyclophosphamide; T=paclitaxel, D=docetaxel, Cb=carboplatin, H=trastuzumab

**Anthracycline (Doxorubicin)**
- Asx LVEF decline: 4% to 11%
- CHF: <1%

**Anthracycline/Trastuzumab**
- Asx LVEF decline: 4% to 19%
- CHF: 2-4%
- Trastuzumab interruption: 5-18%

# Scope of the Problem:
Cardiotoxicity of Non-Anthracycline based Trastuzumab Tx

## Low Cardiac Event Rate

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment Regimen</th>
<th>Asx LVEF ↓</th>
<th>Class III/IV Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dang, et al. JAMA Onc 2016</td>
<td>406</td>
<td>Paclitaxel Trastuzumab</td>
<td>3.2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Jones, et al. Lancet Onc 2013</td>
<td>493</td>
<td>Docetaxel Cyclophosphamide Trastuzumab</td>
<td>5.6%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Slamon, et al. NEJM 2011</td>
<td>1075</td>
<td>Docetaxel Carboplatin Trastuzumab</td>
<td>9.4%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

- Asympt LVEF decline
  - 3.2% to 9.4%
- Class III/IV CHF
  - 0.5%
Dual Anti-HER2 Therapy (Pertuzumab/Trastuzumab)
No increase in cardiac toxicity with addition of pertuzumab to trastuzumab

<table>
<thead>
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<th>Asymptomatic ↓LVEF</th>
<th>Class III/VI Heart Failure</th>
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</thead>
<tbody>
<tr>
<td>NEOSPHERE (Gianni, Lancet 2012)</td>
<td>Docetaxel + trastuzumab</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Docetaxel + trast/pertuzumab</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Docetaxel + pertuzumab</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Pertuz/trastuzumab</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>TRYPHAENA (Schneeweiss, Ann Onc 2013)</td>
<td>FEC+ trast/pertuzumab → docetaxel + trastuz/pertuzumab</td>
<td>5.6%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>FEC→ docetaxel + trast/pertuzumab</td>
<td>5.3%</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td>Docetaxel + carboplatin + trast/pertuzumab</td>
<td>3.9%</td>
<td>0%</td>
</tr>
<tr>
<td>APHINITY (Mickwitz, NEJM 2017)</td>
<td>Chemo + trastuzumab</td>
<td>2.8%</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>Chemo + trastuzumab + pertuzumab</td>
<td>2.7%</td>
<td>0.6%</td>
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FEC = fluorouracil, epirubicin, cyclophosphamide
## Significance of the Problem

**Anthracycline/Trastuzumab Induced Heart Failure: How Important Is it?**

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<th>Study</th>
<th>Rx</th>
<th>NYHA Class III-IV *</th>
<th>Med FU (yrs)</th>
<th>NYHA Class III-IV</th>
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<tr>
<td>HERA¹,²</td>
<td>Chemo → H x 1</td>
<td>0.8 %</td>
<td>11</td>
<td>1.0 %</td>
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<tr>
<td>B-31³,⁴</td>
<td>AC→T</td>
<td>0.8% 4.1%</td>
<td>7</td>
<td>1.0% 4.0%</td>
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<tr>
<td>N 9831⁵,⁶</td>
<td>AC → w T</td>
<td>0.3% 3.3%</td>
<td>9</td>
<td>0.6% 3.4%</td>
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<tr>
<td>BCIRG 006⁷,⁸</td>
<td>AC → D</td>
<td>0.7% 2.0% 0.4%</td>
<td>10</td>
<td>0.7% 2.0% 0.4%</td>
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A=doxorubicin, C=cyclophosphamide; T=paclitaxel, D=docetaxel, Cb=carboplatin, H=trastuzumab; *During Treatment

Retrospective Claims-Based Studies
Significantly Higher Cardiac Event Rates

- N=45,537, mean age of 76 yrs, the 3yr incidence rates of CHF and/or cardiomyopathy\(^1\):
  - Tras: 32%
  - Anthra → Tras: 41.9%

- N=12,5000, mean age of 60 yrs, the 5 yr incidence rates of CHF and/or cardiomyopathy\(^2\):
  - Tras: 12.1%
  - Anthra → Tras: 20.1%

- N=18,540, median age of 54 yrs, the 3 yr incidence rates of CHF/CV death\(^3\):
  - Tras: 5.1%
  - Anthr → Tras: 6.6%

1. Chen et al. JACC 2012
2. Bowles et al. JNCI 20112
3. Thavandiranathan et al. JCO 2016
Significance of the Problem
Anthracycline/Trastuzumab Induced Heart Failure: How Important Is it?

NSABP B-31: cardiac death or CHF 4.0%

Retrospective claim-based study: CM or CHF 20%

Discrepancy in Outcome:
- Claim based data rely on ICD codes
- Clinical trials, strict entry criteria

Clinical Trial Registry, N=2,006
Romond, JCO 2012

Cancer Research Network N=12,500
Bowles EJA Natl Cancer Inst 2012
Radiation Increases Risk of Major Coronary Events in Women After Radiotherapy for Breast Cancer

- 7.4% increase in major coronary events per gray of mean heart dose
Significance of Cardiovascular Disease Among Survivors of Early-Stage Breast Cancer
Ontario Cancer Registry Analyses; N= 98,999 women

- 5+ year survivors >66 years of age:
  - CV mortality exceed that of Breast Cancer

- Patients with prior CV Dx
  - CV mortality (16.9%) > BC mortality (14.6%) at 10 years

Cardiovascular Death: An important competing risk in women with EBC, particularly older women and those with history of CV disease

Abdel-Qadir et al, JAMA Cardiol 2017
Increased CV Mortality in BCA Survivors

7 years after the BC diagnosis: CV death rate greater in BCA than controls.

Bradshaw, Epidemiology 2016; 27; 6-13
Why Does It Happen?
Treatment Related Risks

Anthracyclines → Oxidative Stress (Iron, Top2b, redox cycling) → Myocyte Necrosis → Decreased LVEF/CHF

Trastuzumab → Binding extracellular domain ErbB2, Disabling myocardial cell-protective, repair mechanism → Increased susceptibility of myocyte to cell death induced by anthracyclines

Radiotherapy → Endothelia dysfunction, myocardial fibrosis → Ischemic heart disease, diastolic dysfunction

Tocchetti et al 2012, European Journal of Heart Failure
Why Does It Happen?
Interplay between Anthracycline and Trastuzumab in Cardiac Damage

Anthracycline induced CT:
- Related to cumulative dose
- Occurs within 1 year after tx
- Damage irreversible, generally
- Breast Cancer regimen – doxorubicin, 240 mg/m2

Trastuzumab induced CT:
- Not dose related
- Typically occurs during treatment
- Reversible in majority but not all with halting treatment.

Tocchetti et al 2012, European Journal of Heart Failure
Multiple Hit Hypothesis

Why Does It Happen?

Modifiable lifestyle risk factors (obesity, deconditioning, frailty)
Aging associated comorbid conditions (HTN, DM, increased risk CHD)

Jones L. et al. JACC 2007
Cardio-Oncology Paradigm
Optimize CV and Oncologic Outcomes

Mitigate treatment related adverse cardiac effects; cardioprotection to optimize cardiovascular health

Allow effective cancer treatment (eg avoid dose interruption) to optimize cancer survival
Cardio-Oncology Care Continuum

Cancer Diagnosis

Pre-Treatment
• Identify high risk patients
• Mitigate risk for developing cardiotoxicity
• Inform cancer treatment plan/discussion with oncologist

Start of Treatment

During Treatment
• Monitor cardiotoxicity
• Prevent and manage cardiac events
• Minimize treatment interruptions

End of Treatment

After Treatment
• Monitor increased risk of CV disease
• Optimize long-term CV health
Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Armenian, S et al. JCO 2017

• Before:
  – Assess baseline risk, identify who is at risk
  – Screen and manage modifiable CV risk factors (smoking, HTN, dyslipidemia, DM, obesity)
  – Baseline echo or MUGA/CMR

• During
  – Screen and manage modifiable CV risk factors
  – H & P, signs/symptoms of cardiac dysfunction → refer to cardiologist, ECHO (or CMR/MUGA), cardiac biomarkers, strain imaging
  – Surveillance ECHO monitoring for pts at increased risk

• After
  – H&P, signs/symptoms of cardiac dysfunction → refer to cardiologist, ECHO (or CMR/MUGA), cardiac biomarkers
  – ECHO at 6-12 mo post-Rx for pts at increased risk
Trastuzumab Cardiotoxicity
Clinical Risk Factors

- Pretreatment with Anthracyclines
- EF<55% prior to trastuzumab
- Older age
- Hypertension
- Elevated BMI
- Coronary artery disease
- Atrial fibrillation
- Renal disease

Suter JCO 2007
Romond JCO 2012
Guenancia JCO 2016
Ezaz JAHA 2014
Impact of CV risk factors on cardiac events and survival outcomes among survivors of breast cancer

- 1,460 Participants >66 yo, from 5 SWOG breast cancer trials, 1999-2011, high prevalence of HTN (73%) and hyperlipidemia (57%)

- Baseline CV risk factors associated with:
  - increased risk of death
  - worse progression free survival
  - worse cancer survival.
  - increased risk of cardiac events with each additional CV risk factor

Hershman D, J Clin Oncol 2018
ASCO Clinical Practice Guideline:
Which patients with breast cancer are considered at increased risk for developing cardiac dysfunction?

- Low dose anthra* (ie: AC→T) or Tras alone (ie: TH) with any of the following risk factors:
  - > 2 risk factors: smoking, HTN, dyslipidemia, DM, obesity
  - Age ≥ 60 y/o
  - Compromised cardiac function: LVEF of 50-55%, h/o MI, > moderate valvular disease

- Low dose anthr* → tras (ie: AC→ TH)

*Doxorubicin < 250 mg/m², Epirubicin < 600 mg/m²
A=doxubicin, C=cyclophosphamide, T=taxane, H=trastuzumab

Armenian et al. JCO 2017
Case#1: Cardiology Visit

Pt History:
- Cancer Diagnosis and Treatment: High risk BC planned for anthracycline followed by trastuzumab
- Age: ≥ 60 yo
- Cardiovascular Risk Factors
  - Hypertension on HCTZ alone,
  - Hyperlipidemia, not on statin
  - DM on metformin
  - Obesity and sedentary lifestyle
- Asymptomatic at low levels of physical activity. No ischemic or HF symptoms
- PE: BP 165/90 mm Hg, HR 85, 98% O2 saturation, RR 15. BMI 31. Normal cardiac exam
- Baseline Echo: normal LVEF 64%, Grade I diastolic dysfunction, no valvular disease

Pre-Treatment Assessment:
- Assess risk for developing cardiac dysfunction
  - High risk – based on tx, age, risk factors
- Identify and Manage CV Risk Factors
  - Hypertension
    - Aggressive BP control, home BP monitoring; target <130/80 mm Hg, switch HCTZ to ACE/ARB or carvedilol
  - Diabetes
    - Optimize glycemic control, HgbA1C<7%
  - Hyperlipidemia – Follow ACC/AHA CV risk
    - Start lipitor/crestor
  - Sedentary lifestyle and Obesity
    - Encourage increase activity and dietary modifications
- Evaluate for clinical CV disease
  - No clinical evidence
• Patient starts treatment...
• How should we monitor cardiotoxicity during therapy?
## Guidelines on Cardiac Monitoring Before, During and After Trastuzumab Therapy

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
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<td>LVEF assessment every 3 months (during trastuzumab)</td>
<td>LVEF measurement every 6 months for at least 2 years after completion</td>
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<td><strong>European Association of</strong></td>
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<td><strong>Imaging (EACVI), 2014</strong></td>
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<td><strong>National Comprehensive</strong></td>
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<td>Consider within 12 months of anthracyclines in <em>patients with CV risk factors</em>¹</td>
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¹HTN, dyslipidemia, DM, FH of cardiomyopathy, Age > 65, ≥ 300mg/m² doxorubicin, smoking, alcoholism, obesity, low normal LVEF at baseline

²≥250mg/m² doxorubicin, high dose RT (> 30Gy), ≥ 2 CV risk factors (smoking, HTN, DM, HL, obesity), age > 60, pre-existing structural heart disease, sequential anthracyclines + trastuzumab

Modified from Liu, Thavendiranathan, Barac, JACC Imaging 2018
FDA Trastuzumab Package Insert

Monitoring Recommendations

**BASELINE MEASUREMENT**
Immediately prior to initiation of trastuzumab

**EVERY 3 MONTHS**
During and upon completion of trastuzumab

**EVERY 6 MONTHS**
*For at least 2 years following completion of trastuzumab

- Pre-Chemotherapy
- Pre-Trastuzumab
- 3 months
- 6 months
- 9 months
- 12 months

- **Doxorubicin**
- **Cyclophosphamide**

Trastuzumab
Every 3 weeks

Courtesy of Dr. Yu
Current Cardiac Surveillance Guideline: Too Much, Too Little, or Just Right?

1. FDA monitoring scheme challenged as appropriate for all patients receiving trastuzumab therapy.

2. Is there potential harm with excessive monitoring?
   - Rx interruption, financial cost

3. Should cardiac monitoring frequency be tailored to patient- and treatment-specific risk factors?

4. Absence of prospective studies that link adherence with cardiac monitoring to heart failure outcomes.

### Guidelines on Cardiac Monitoring Before, During and After Trastuzumab Therapy

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Modified from Liu, Thavendiranathan, Barac, JACC Imaging 2018
Case #2

- 54 yo female who presented 3 years ago with a right breast mass. After evaluation, she was noted to have stage 2 HER2-positive, hormone receptor negative breast cancer. She underwent R mastectomy/axillary sentinel node biopsy, followed by adjuvant anthracycline/taxane/trastuzumab and post-mastectomy radiation.

- She did well for 3 years, but then presented with back pain.
- Imaging revealed bony metastatic disease and liver metastases.
- Liver biopsy showed metastatic breast cancer, HER2-positive and ER negative.
Case #2 continued

• PMH: none
• Meds: none
• SH: no tobacco, alcohol, drugs
Audience Response Question #3

Which regimen is recommend for first line therapy for HER2-positive metastatic breast cancer?

A. Paclitaxel/trastuzumab (TH)
B. Docetaxel/trastuzumab/pertuzumab (THP)
C. Doxorubicin/Cyclophosphamide (AC)
D. Trastuzumab/lapatinib
Audience Response Question #3

Which regimen is recommend for first line therapy for HER2-positive metastatic breast cancer?

A. Paclitaxel/trastuzumab (TH)
B. Docetaxel/trastuzumab/pertuzumab (THP)
C. Doxorubicin/Cyclophosphamide (AC)
D. Trastuzumab/lapatinib
Approach to Treating Metastatic Breast Cancer

- Treatment goal: long-term cancer control

1st Line Palliative Therapy

**Check Scans**

- Check toxicity

- No progression/Tolerable

Continue Therapy

Try Another Treatment

Etc.
### Pivotal Phase III Trastuzumab Studies in Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy Alone</th>
<th>Chemotherapy + Trastuzumab</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slamon: Paclitaxel or Anthracycline-based*</td>
<td>20.3</td>
<td>25.1</td>
<td>0.80 (0.64-1.00)</td>
<td>0.046</td>
</tr>
<tr>
<td>Marty: Docetaxel</td>
<td>22.7</td>
<td>31.2</td>
<td>Not reported</td>
<td>0.0325</td>
</tr>
</tbody>
</table>

*Patients previously treated with adjuvant anthracyclines received paclitaxel and patients not previously treated with anthracyclines received doxorubicin/cyclophosphamide.

Overall, the addition of trastuzumab to chemotherapy improves overall survival in metastatic breast cancer.
**1st Line Pertuzumab for Metastatic HER2-Positive Breast Cancer**

**CLEOPATRA TRIAL:**

HER2-positive locally recurrent, unresectable or MBC

≤ 1 hormonal regimen for MBC

Prior (neo)adjuvant systemic Rx, including trastuzumab and/or taxane allowed if followed by DFS ≥ 12 mos

Baseline LVEF ≥ 50%; no CHF or LVEF < 50% during or after previous trastuzumab

---

**Primary endpoint:** Independently assessed PFS

---

**CLEOPATRA TRIAL:****

- **Docetaxel**
  - **Trastuzumab**
  - **Placebo**

- **Docetaxel**
  - **Trastuzumab**
  - **Pertuzumab**

---

CLEOPATRA Trial Survival Results

Median OS:
THP: 56.5 mo
TH: 40.8 mo
HR 0.68
P<0.001
Case #2: Treatment Course

- She initiates therapy with docetaxel/trastuzumab/pertuzumab
- No cardio-oncology referral at baseline
- Baseline EF 60%
- 3 months later, repeat echo shows EF 45%
- Scans at that time show she is responding to therapy.
- Treatment held; referral to cardio-oncology
Case #2 - Cardiology Visit

Pt History:
- Age: 54 yo
- Cancer Diagnosis and Treatment: metastatic BC planned trastuzumab/pertuzumab tx w/goal of long term cancer control
- Cardiovascular Risk Factors
  - None
- Asymptomatic
  - No ischemic or HF symptoms
- PE: BP 120/73 mm Hg, HR 85, 98% O2 saturation, RR 15. Normal cardiac exam
- Cardiac Monitoring:
  - Pre-Tx Echo: LVEF 60%; F/U surveillance echo 45%

Assessment:
- Risk for cardiac events
  - Not high risk
- Identify and Manage CV Risk Factors
  - N/A
- Evaluate for clinical CV disease
  - None
Question:
What are the treatment options when LVEF decline occurs during treatment?
Management of Asymptomatic LVEF Decline During Trastuzumab Therapy: Halt or Continue Tx?

FDA Trastuzumab Package Insert
Recommendations for Trastuzumab Rx

• **Withhold** for ≥ 4 weeks if LVEF decline
  – ≥ 16% from baseline
  – ≥ 10% from baseline to < LLN
  – Repeat LVEF monitoring in 3-4 weeks

• **Resume** if LVEF improves above LLN with absolute decrease from baseline ≤ 15%

“The safety of continuation or resumption of Trastuzumab in patients with Trastuzumab induced LV dysfunction has never been studied.”

https://www.herceptin.com
4.4 No recommendations can be made regarding continuation or discontinuation of cancer therapy in individuals with evidence of cardiac dysfunction. This decision, made by the oncologist, should be informed by close collaboration with a cardiologist, fully evaluating the clinical circumstances and considering the risks and benefits of continuation therapy responsible for the cardiac dysfunction.
Treatment of Asymptomatic LV dysfunction
Management of Heart Failure
ACCF/AHA Guideline
Is continuing trastuzumab therapy safe in asymptomatic mild LVEF decline?

- **SAFEHEART Study:**
  - Pilot study, N = 30 pts with LVEF ≥ 40% and < 50% and no symptoms of HF
  - Primary endpoint
    - Completion of the planned HER2 therapy without a cardiac event (HF, MI, arrhythmia, cardiac death, or significant worsening of LVEF).
  - All pts underwent cardiology visits, serial echos, taking BB and ACEI
  - 90% (27 pts) completed the planned trastuzumab therapy without cardiac event.

Barac A, Smith K..., Swain S, JCO 2018
Is continuing trastuzumab therapy safe in asymptomatic mild LVEF decline?

• 31 patients with asymptomatic LVEF decline during trastuzumab
  – 9 with LVEF decline > 10% from baseline to below LLN
  – 22 with LVEF decline > 16% from baseline
• All patients completed trastuzumab without interruption.
• No patients developed HF during continued trastuzumab.

Trastuzumab continuation may be safe in patients who develop a LVEF decline but with LVEF that remains above 50%.

Returning to Case #2

- After discussion with the oncologist and informing the patient of the risks/benefit of continuing treatment, a decision made to continue treatment with close cardiac monitoring.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 mos Tx</th>
<th>4.5 mos Tx</th>
<th>6 mos Tx</th>
<th>9 mos T</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF %</td>
<td>60%</td>
<td>45%</td>
<td>50%</td>
<td>52%</td>
<td>50%</td>
</tr>
<tr>
<td>GLS%</td>
<td>-20.2%</td>
<td>-15.4%</td>
<td>-16.8%</td>
<td>-16.5%</td>
<td>-16.5%</td>
</tr>
</tbody>
</table>

- Started carvedilol
## Could Cardiotoxicity be Prevented with Cardiac Medications?

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Cancer Treatment</th>
<th>Intervention Study Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRADA</strong>¹</td>
<td>All epirubicin, 22% trastuzumab</td>
<td>2 x2 metoprolol and candesartan</td>
<td>LVEF ↓ 0.8% w/ candesartan vs. 2.6% w/ placebo (CMR)</td>
</tr>
<tr>
<td>N=130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MANTICORE</strong>²</td>
<td>All trastuzumab; 33% anthracycline</td>
<td>1:1:1 bisoprolol, perindopril, placebo</td>
<td>LVEF ↓1% w/ bisoprolol vs 3% w/ perindopril vs 5% w/ placebo (CMR)</td>
</tr>
<tr>
<td>N=94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CECCY</strong>³</td>
<td>All doxorubicin</td>
<td>1:1 carvedilol and placebo</td>
<td>No difference in LVEF decline &gt;10% (13.5% vs. 14.5%) (Echo)</td>
</tr>
<tr>
<td>N=200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>USF study</strong>⁴</td>
<td>All trastuzumab; 40% anthracycline</td>
<td>1:1:1 carvedilol, lisinopril, placebo</td>
<td>No difference in LVEF decline &gt;10% (30% lisinopril vs. 29% carvedilol vs. 32% (Echo)</td>
</tr>
<tr>
<td>N=486</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Gulati et al, Eur Heart J 2016; ² Pituskin et al, J Clin Oncol 2017; ³ Avila MS et al. JACC 2018; ⁴ Guglin M et al. ACC presentation 2018
Cardiotoxicity-free survival for the cohort with Trastuzumab exposure with and without anthracyclines

Entire cohort: Trastuzumab +/- Anthracycline

Decrease in LVEF >10%: 30% w/ lisinopril vs. 29% w/ carvedilol vs. 32% w/ placebo (p = NS)

Guglin M. et al, ACC 2018 Abstract Oral Presentation

Trastuzumab w/ Anthracycline

Decrease in LVEF >10%: 37% w/ lisinopril vs. 31% w/ carvedilol vs. 47% w/ placebo (p = 0.009)
Conclusion

• Important to assess and manage CV risk factors in patients prior to and during potentially cardiotoxic therapy.

• To optimize oncologic and cardiac outcomes:
  – Avoid/minimize treatment interruptions of life saving therapy
  – Mitigate cardiac events with aggressive CV risk factor modification

• Need better risk stratification tool to tailor cardiac surveillance during treatment, based on patient- and treatment-specific risk factors

• Close collaboration between Oncologists and Cardiologists essential