Case Study in Cancer and Cardiotoxicity

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Case Study

54 Y/O Black female with Metastatic Breast Ca
ER/PR Neg, Her-2-Neu Positive
Presents with mild, DOE/SOB with Daily activity
History of HTN/Dyslipidemia (SBP120-130mmHg)
Treatment:
Lisinopril/HCTZ-20/12.5mg daily
Simvastatin-40mg Daily
(no troponin or BNP at baseline)
Echocardiogram 4/11, LVEF=58%-2D/MOD
LVPWTD-1.3cm(NL<1.1)
Case Study

How would you classify the cardiovascular risk of this patient prior to treatment of her breast cancer?

A) No risk
B) Low Risk
C) Moderate Risk
D) High Risk
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# Heart Failure Classifications

## Classification of Heart Failure (HF)

<table>
<thead>
<tr>
<th>Examples</th>
<th>ACC/AHA HF stage (Evolution and progression)</th>
<th>NYHA Functional Class (Severity of symptoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A At high risk for developing HF</td>
<td>I Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>No structural heart abnormality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Has never shown signs or symptoms of HF</td>
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<tr>
<td></td>
<td></td>
<td>II HF symptoms with ordinary exertion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III HF symptoms with minimal exertion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV Symptoms at rest</td>
</tr>
<tr>
<td>Hypertension; coronary artery disease; diabetes mellitus; history of rheumatic fever or cardiotoxic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV hypertrophy, fibrosis, dilatation or hypocontractility; asymptomatic valvular disease; previous MI</td>
<td>Structural disorder of the heart. Has never shown signs or symptoms of HF</td>
<td></td>
</tr>
<tr>
<td>Dyspnea or fatigue due to LV systolic dysfunction; asymptomatic patients in treatment for prior symptoms of HF</td>
<td>Underlying Structural disorder of the heart. Has current or prior symptoms of HF</td>
<td></td>
</tr>
<tr>
<td>Hospitalized for HF and cannot be safely discharged; in hospital awaiting transplantation; continuous intravenous support; mechanical circulatory assist device; in hospice setting for HF treatment</td>
<td>Advanced Structural disorder of the heart. Refractory HF, symptoms at rest despite medical therapy Requires specialized interventions</td>
<td></td>
</tr>
</tbody>
</table>


Case Study

What if any changes would you make prior to starting her Trastuzumab?

A) None Proceed with chemo, immediately
B) Discontinue ACE/HCTZ and start CCB
C) Discontinue ACE/HCTZ and Start Carvedilol/Toprol XL
D) Discontinue ACE/HCTZ, Start Carvedilol/Toprol XL and proceed with further evaluation
CV Mortality Risk *Doubles* With Each 20/10 mmHg Increase in BP

**SBP/DBP, mmHg**

- **115/75** (RR = X1)
- **135/85** (RR = X2)
- **155/95** (RR = X4)
- **175/105** (RR = X8)

BP = blood pressure.

*Individuals aged 40–69 years (N=1 million).*

Treatment Plan

- Started on Taxol/Trastuzumab Weekly on 4-25-11
- FEC/Trastuzumab 2 Cycles
- BP148/95mmHg (No documented BP of less than 148/95 throughout her treatment)
- Cardiology consult on 9-16-11
- BNP=124
- Trop=0.04 (NL=0.00-0.03)
- TSH=NL
Small Reductions in BP May Result in Large Risk Reductions for CV Events

- Meta-analysis of 61 prospective, observational studies
- 1 million adults
- 12.7 million person-years

2 mm Hg decrease in mean SBP

- 7% reduction in risk of IHD*
- 10% reduction in risk of stroke mortality

*IHD=ischemic heart disease

Plan:

1) Lasix 40mg daily times two days

2) A Left Heart Cath/Selective Angio/Right Heart Cath/Endomyocardial Biopsy performed

- Normal coronaries
PAP-NL, PCWP=10

Endomyocardial sample for Myocarditis (Parvo virus, etc), Evaluation of Cardiac injury from Adriamycin, extent of ultrastructural injury of myocytes
Comparison of Cardiac Biopsy Grades and LVEF Estimations in Patients Receiving Adriamycin

- Evaluated 158 Patients with exposure to adriamycin with EMB
- Correlation with cumulative adriamycin dose and biopsy grade.
- Poor correlation between changes in biopsy grade and LVEF
- Change in resting LVEF detected by echocardiography did not predict biopsy grade
- Structural changes precede the fall in ejection fraction

JCO :2; 1984
4-11 LVEF = 59%

9-16 LVEF = 45%

Absolute 14 Point drop in LVEF
9-16-LVEF=45%

9-30- LVEF=58%
3D Left Ventricular Function
LVEF at baseline and with trastuzumab in a selected patient population
(referred for possible chemotherapy induced LV dysfunction)
Case Study

What Recommendations would you make to oncologist?

A) Hold Trastuzumab indefinitely

B) Hold Trastuzumab, resume when LVEF >55%

C) Rapid increase in Carvedilol/Toprol XL and resume Trastuzumab on scheduled 3 week dose.

D) Switch to Lapatinib
Comparison of LVEF at Baseline and After Chemotherapy

Data expressed as mean values.

Kalay et al. JACC. Dec 2006. 48:2258-62
Table 1: Comparison of Echocardiographic Parameters in the Study Group Between Baseline and Follow-Up Values

<table>
<thead>
<tr>
<th></th>
<th>Statin Group (n = 20)</th>
<th>Control Group (n = 20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>61.3 ± 7.9</td>
<td>62.9 ± 7.0</td>
<td></td>
</tr>
<tr>
<td>After 6 months</td>
<td>62.6 ± 9.3</td>
<td>55.0 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>1.3 ± 3.8</td>
<td>−7.9 ± 8.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>46.5 ± 7.2</td>
<td>47.2 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>After 6 months</td>
<td>46.3 ± 6.8</td>
<td>49.2 ± 6.2</td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>−0.15 ± 4.0</td>
<td>2.0 ± 3.3</td>
<td>0.021</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>30.9 ± 7.2</td>
<td>30.3 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>After 6 months</td>
<td>29.6 ± 6.1</td>
<td>32.3 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>−1.35 ± 4.0</td>
<td>2.1 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter.

Randomized Lipitor 40mg daily/Total dose doxo=251mg, one cycle per month X 6 months

JACC Vol 58:2011
Binding to specific adrenergic receptors, β-blockers inhibit cancer cell migration and metastasis, suggesting a novel targeted therapeutic application in protecting against breast cancer disease progression.
### Beta Blockers are Beneficial in Patients with Metastatic Breast Cancer

Table 5. Multivariable Cox Proportional Hazards Model for All Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relapse-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Beta-blocker use, yes vs no</td>
<td>0.52</td>
<td>0.31 to 0.88</td>
</tr>
<tr>
<td>Age, ≥ 50 vs &lt; 50 years</td>
<td>0.81</td>
<td>0.66 to 1.00</td>
</tr>
<tr>
<td>Race, black vs non-black</td>
<td>1.37</td>
<td>1.06 to 1.77</td>
</tr>
<tr>
<td>Stage, III vs I/II</td>
<td>1.70</td>
<td>1.38 to 2.08</td>
</tr>
<tr>
<td>Grade, III vs I/II</td>
<td>1.18</td>
<td>0.92 to 1.53</td>
</tr>
<tr>
<td>Hormone receptor status, positive vs negative</td>
<td>0.74</td>
<td>0.48 to 1.13</td>
</tr>
<tr>
<td>HER2 status, positive vs negative</td>
<td>1.31</td>
<td>0.92 to 1.87</td>
</tr>
<tr>
<td>Triple-negative tumor, no vs yes</td>
<td>0.71</td>
<td>0.44 to 1.14</td>
</tr>
<tr>
<td>LVI, positive vs negative</td>
<td>1.89</td>
<td>1.54 to 2.32</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-29 vs &lt; 25</td>
<td>0.99</td>
<td>0.77 to 1.27</td>
</tr>
<tr>
<td>30+ vs &lt; 25</td>
<td>1.16</td>
<td>0.9 to 1.50</td>
</tr>
<tr>
<td>Diabetes, yes vs no</td>
<td>1.20</td>
<td>0.77 to 1.88</td>
</tr>
<tr>
<td>Hypertension, yes vs no</td>
<td>1.08</td>
<td>0.8 to 1.45</td>
</tr>
<tr>
<td>ACEI/ARB use, yes vs no</td>
<td>0.82</td>
<td>0.54 to 1.26</td>
</tr>
</tbody>
</table>

Abbreviations: LVI, lymphovascular invasion; BMI, body mass index; HER2, human epidermal growth factor receptor 2; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Baseline Hypertensive BC Patients Treated with Beta Blockers Live Longer

Figure 1a: Hypertensive BC patients therapeutically treated with beta-blockers showed significantly (p=0.022) longer times before acquiring metastases compared to non-treated patients.

Figure 1b: Hypertensive BC patients receiving beta-blocker therapy showed significantly (p=0.011) improved 10 year survival rates compared to non-treated patients.

Oncotarget 2010; 1:628-638
Oncologist Perspective on Disease Management

New Cancer Diagnosis
Image and Biopsy

Identify Molecular and Genetic Targets From Biopsy sample

Perform Cytogenetics and Identify Markers for measuring response

Treat tumor based on Markers and identify most likely hematologic and cytogenetic markers to predict response/remission/recurrence/survival
Current Perspective for Left Ventricular Systolic Dysfunction Treatment

Identify New Onset LV Systolic Dysfunction
Cardiac Imaging
BNP/Trop
Symptomatic or asymptomatic

Look for other causes of LV Systolic dysfunction
“rarely Biopsy”

Start Medical therapy with ACE-I/ARB/BB

Repeat Imaging Studies
If improved, continue therapy
Treatment Failure: AICD/CRT LVAD/Transplant Death
New Paradigm for Chemotherapy Prognosis and Treatment

- New LV Systolic heart Failure from Chemotherapy
  - Identify SNP’s and Microarray Which Predicts Response to medical therapy/prognosis/Survival From Blood/Biopsy sample
- Measure Markers for predicting response
- Treat Chemotherapy-induced systolic Heart Failure based on unique hematologic and microarray markers to predict response/recovery/recurrence/survival
  - Also Platform for new therapeutic targets