Cardiotoxicities of Contemporary Cancer Treatment

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Which of the following is true about HER2 targeted therapy and LV dysfunction?

A. Once LVEF <50%, need to permanently discontinue treatment
B. LVEF recovers in about 60% of cases
C. It is safe to continue treatment despite drop in LVEF to 40% range if there is no clinical heart failure
D. HER2 treatment associated cardiotoxicity can present decades after exposure
Which of the following is true about ponatinib?

A. Significant hypertension is uncommon
B. Ponatinib has a safer CV side effect profile compared to imatinib
C. Arterial vascular disease is a potential side effect
D. Ponatinib increases QTc significantly
1. Discuss how to manage LV dysfunction from anthracyclines and HER2 targeted therapies
2. Recognize cardiovascular side effects of TKI’s
3. Highlight future directions in cardio-oncology
Cardiac effects of chemotherapy: Beyond LV function

- **Platinum based therapies**
- **Antimetabolites**
- **Radiation**

**Multitargeted TKI and VEGF-inhibitors**

- **Her2-targeted Therapies**
- **Proteosome inhibitors**
- **Anthracyclines**
- **Alkylating Agents**

- **Thalidomide**
- **Microtubule Inhibitors**

Cardiomyocyte damage and heart failure

Hypertension

Ischemia vascular effects

Coronary disease

Valvular disease

Pericardial disease

Anrhythmias
ICOS 2022 definitions for cardiotoxicity

Cardiac Dysfunction/HF
Cardiac dysfunction or structural injury associated with cancer therapy, which can remain asymptomatic, or present as clinical HF, each defined ranging from mild to severe degree
(Table 1, Figure 2)

Myocarditis
Toxicity or immune-mediated inflammation of the myocardium, associated with various cancer therapies, especially immune checkpoint inhibitors, defined by major and minor diagnostic criteria
(Table 2)

Arrhythmias/QT Prolongation
A QT interval >500 ms, measured by the Fridericia formula, is defined as prolonged. Supraventricular and ventricular arrhythmias are defined as per standard practice
(Table 5, Figure 3)

Definition of Key Cardiovascular Toxicities

Hypertension
Elevation in systolic and/or diastolic blood pressure after initiation of cancer therapy without any other contributing changes.
130/80 mmHg and 140/90 mmHg are defined as diagnostic and therapeutic thresholds according to co-morbidities
(Table 4)

Vascular Toxicity
Induction or aggravation of vascular disease caused by cancer therapy; vascular toxicity may be transient or sustained, symptomatic or asymptomatic, defined by standard criteria
(Table 3)
JC: 35 y/o woman, no PMH
Dx: Infiltrating lobular carcinoma of L breast, ER-/PR-, HER2+, no mets

What is her risk of cardiotoxicity?

Lumpectomy, Radiation therapy, ddAC-T (doxorubicin, cyclophosphamide and paclitaxel)
HER2+ → Starts trastuzumab 1 mo later
Breast cancer in remission
Anthracycline cardiotoxicity

Doxorubicin dose | Incidence of LV dysfunction
--- | ---
400 mg/m² | 3-5%
550 mg/m² | 7-26%
700 mg/m² | 18-48%
Anthracyclines and types of cardiotoxicities

- **Acute**: Within 2 weeks from treatment
- **Early-onset**: Within 1 year. Most frequent form of CTX
- **Late-onset**: Years to decades later

Incidence of cardiotoxicity 9%
98% occurred within first year

Anthracycline cardiotoxicity is reversible?

11% patients had full recovery
71% patients had partial recovery
Timing of intervention matters

201 patients with LVEF < 45% due to anthracyclines
Enalapril and carvedilol were added, followed LVEF q3 mo

Time between chemo and HF meds

Earlier is Better!

Early = Response = Survival!

Cardinale D et al. JACC. 2010; 55:213-20
# Trastuzumab Cardiotoxicity

<table>
<thead>
<tr>
<th>Selected Trials</th>
<th>Time interval between anthracycline and trastuzumab</th>
<th>Incidence of CHF (%)</th>
<th>Incidence of LV dysfunction (%)</th>
<th>Reversibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slamon <em>et al.</em>‡</td>
<td>Concurrent</td>
<td>16</td>
<td>27</td>
<td>Yes</td>
</tr>
<tr>
<td>NCCTG N9831; arm B</td>
<td>105 days</td>
<td>2.8</td>
<td>7.8</td>
<td>Yes</td>
</tr>
<tr>
<td>NCCTG N9831; arm C</td>
<td>21 days</td>
<td>3.3</td>
<td>10.4</td>
<td>Yes</td>
</tr>
<tr>
<td>BCIRG-006; Anthracycline arm</td>
<td>21 days</td>
<td>2.0</td>
<td>18.6</td>
<td>Yes</td>
</tr>
<tr>
<td>BCIRG-006; Nonanthracycline arm</td>
<td>NA</td>
<td>0.4</td>
<td>9.4</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- Administration w/ anthracyclines increases risk
- Increased delay between therapies decreases risk
- Toxicity is usually reversible

Modified from: Ewer MS and Ewer SM. Nat Rev Cardiol. 2015. 12. 547-58
What about trastuzumab rechallenge?

38 patients with HER2/neu+ breast cancer
All received anthracyclines

![Graph showing mean LVEF (%)]

Prior to trastuzumab

After trastuzumab

Ewer MS et al. JCO 2005. 23: 7820-26
Case study: Breast cancer

- Echo shows LVEF of 40% (baseline 60%)
- GLS is now -13% (baseline -19%)

Could we have prevented this?
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Cohort and Exposure</th>
<th>Cardiac Intervention</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OVERCOME</strong></td>
<td>2013</td>
<td>Hematologic malignancies (AML or auto–HSCT)</td>
<td>Enalapril and carvedilol vs. placebo</td>
<td>Change in LVEF on echo and cardiac MRI</td>
<td>Enalapril and coreg prevented drop in LVEF; also lower incidence of death or HF</td>
</tr>
<tr>
<td><strong>PRADA</strong></td>
<td>2016</td>
<td>Early stage breast cancer treated with anthracyclines +/- trastuzumab or RT</td>
<td>2x2 factorial treatment with candesartan or metoprolol succinate vs. placebo</td>
<td>5% drop in LVEF by cardiac MRI</td>
<td>Candesartan attenuated drop in LVEF (0.8% vs. 2.6%); no effect of metoprolol succ</td>
</tr>
<tr>
<td><strong>MANTICORE</strong></td>
<td>2017</td>
<td>HER2-positive early breast cancer +/- anthracyclines</td>
<td>Perindopril vs. bisoprolol vs. placebo</td>
<td>Change in LVEDVi (primary) and LVEF (secondary, LVEF ≥ 10% drop to less than 53%) by cardiac MRI</td>
<td>No difference in LVEDVi; bisoprolol (-1%) and perindopril (-3%) protected against change in LVEF vs. placebo (-5%)</td>
</tr>
<tr>
<td><strong>CECCY</strong></td>
<td>2018</td>
<td>HER2-neg breast cancer exposed to anthracyclines</td>
<td>Carvedilol vs. placebo</td>
<td>≥ 10% drop in LVEF by echo</td>
<td>No difference in LVEF or BNP between groups; carvedilol protected against troponin elevation and diastolic dysfunction</td>
</tr>
<tr>
<td><strong>USF (Guglin)</strong></td>
<td>2018</td>
<td>Breast cancer exposed to trastuzumab +/- anthracyclines</td>
<td>Lisinopril vs. carvedilol vs. placebo</td>
<td>≥ 10% drop in LVEF by echo</td>
<td>No difference in trastuzumab alone; for those exposed to anthracyclines and trastuzumab, lisinopril and carvedilol were protective</td>
</tr>
<tr>
<td><strong>ICOS-One</strong></td>
<td>2018</td>
<td>Mixed cohort with exposure to anthracyclines</td>
<td>Enalapril starting with anthracyclines vs. only starting with Troponin elevation</td>
<td>Troponin elevation</td>
<td>No difference between strategy of primary prevention vs. Troponin-triggered strategy</td>
</tr>
</tbody>
</table>

OVERCOME: Bosch X et al. JACC 2013; 61(23): 2355-62
MANTICORE: Pituskin et al. JCO 2017; 35(8): 870-7
CECCY: Avila MS et al. JACC 2018; 71(20): 2281-90
USF: Guglin M. Presented at ACC 2018, NCT01009918
Meta-analysis of NH blockade as cardioprotection

Patients With Cancer Undergoing Chemotherapy

Cardiotoxicity, Subclinical Cardiac Dysfunction, and Heart Failure

Neurohormonal Therapies
- β-blockers
- ACE inhibitors/ARBS
- mineralocorticoid receptor antagonists

Updated Trial-Level Meta-Analysis
17 Studies

Vaduganathan M et al. JACCCO 1(1): Sept 2019
Meta-analysis of NH blockade as cardioprotection

Key Findings
- 3.96% (95% CI: 2.90% to 5.02%) absolute attenuation in LVEF decline with neurohormonal therapies

Caveats in Interpretation
- Small, single or few center experiences
- Publication bias
- Wide heterogeneity in treatment effect estimates
- Uncertain clinical meaningfulness of short-term LVEF changes

Unmet Need
- Large randomized clinical trials powered to detect treatment effects on clinical outcomes

Vaduganathan M et al. JACC 1(1): Sept 2019
What about statins?

- Stage I-III breast CA or stage I-IV lymphoma
- Chemotherapy w/ anthracycline
- 279 randomized to atorvastatin 40 mg vs placebo
- Followed for 24 months
- Primary endpoint change in LVEF on CMR

Subgroup analyses

Risk ratios for greater than 5 percentage decline in LVEF over 24 months

Meta-analysis of dexrazoxane in BC

**CENTRAL ILLUSTRATION** Dexrazoxane in Breast Cancer Patients Under Anthracycline-Based Chemotherapy

9 STUDIES

2,177 Breast Cancer Patients Treated with Anthracyclines

Patients Treated With Dexrazoxane

- Dexrazoxane reduced the risk of clinical heart failure (RR = 0.19 (95% CI: 0.09 to 0.40), p <0.001) and cardiac events (RR = 0.36 (95% CI: 0.27 to 0.49), p <0.001)

- The rate of partial or complete oncological response, overall survival, and progression-free survival were not affected by dexrazoxane

Patients Treated Without Dexrazoxane

Macedo AV et al. JACC. Cardio-oncology 2019 1(1)
Case study: JC

- Trastuzumab held; Started carvedilol and lisinopril
- 1 month later: LVEF 60% (GLS -18%)
- Completed Trastuzumab, LVEF stable
What about long term risk?

**FIGURE 2** HF Hospitalizations After Breast Cancer

Kaiser Pathways – Incident CVRF

CUMULATIVE INCIDENCE* AT 2 YEARS AND 5 YEARS OF CVD RISK FACTORS

Case  Control

HYPERTENSION

2 YEARS  14.4  10.4
5 YEARS  21.8  19.2

DIABETES

2 YEARS  2.9  2.0
5 YEARS  6.6  5.2

DYSLIPEDEMIA

2 YEARS  12.4  11.6
5 YEARS  21.4  21.6

ANY

2 YEARS  21.5  16.5
5 YEARS  31.4  30.4
Summary: anthracyclines +/- HER2

- Anthracycline cardiotoxicity
  - Dose dependent (risk at 200 mg/m²; stop at 550 mg/m²)
  - Occurs mostly within 1 year, partially reversible

- HER2 targeted therapy cardiotoxicity
  - Not dose related
  - Always reversible; Rechallenge is well-tolerated

- Beta blockers and ACEi may be cardioprotective for primary prevention – but unclear which patients

- Think about long-term risk and surveillance for CV disease but also cardiometabolic disease (HTN, T2DM)
Which of the following is true about HER2 targeted therapy and LV dysfunction?

A. Once LVEF <50%, need to permanently discontinue treatment

B. LVEF recovers in about 60% of cases

C. It is safe to continue treatment despite drop in LVEF to 40% range if there is no clinical heart failure

D. HER2 treatment associated cardiotoxicity can present decades after exposure
Case 2: CML and BCR-ABL TKI

- Diagnosed at age 71 with CML without significant PMH
  - Treated w/ imatinib → stopped due to ocular symptoms
  - Treated w/ dasatinib → pleural effusions
  - Switched to nilotinib → good response but LE claudication with stenosis of bilateral SFA and L PTA
  - Switched to bosutinib

- Ongoing hypertension, progressive aortic stenosis
Considerations of oral targeted therapies

Oral Antineoplastic Agent

Baseline CV Risk Assessment

CV Adverse Event

CV Monitoring

CV Management

LV Dysfunction/Heart Failure

Careful H and P
LVEF by 2D/3D Echo/cMRI

- Rule out other causes
- Consider ACE-I/ARB/BB for LV dysfunction or high risk patients

### BCR-ABL TKI-related cardiovascular toxicities

<table>
<thead>
<tr>
<th></th>
<th>HTN</th>
<th>↑QTc</th>
<th>AF</th>
<th>HF</th>
<th>HG</th>
<th>DL</th>
<th>Peric-E</th>
<th>Pleu-E</th>
<th>PH</th>
<th>VascTox</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st generation BCR-ABL TKI</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Imatinib</td>
<td>○</td>
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- **Very common**: ≥10% incidence
- **Common**: 1% to <10% incidence
- **Uncommon**: 0.1% to <1% incidence
- **Rare**: <0.1% incidence

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*2022 ESC Guidelines on cardio-oncology*
Hypertension from VSP inhibitors

Proposed Mechanisms of VSP-Inhibitor Hypertension

- Increased Endothelin-1 Production
- Decreased Nitric Oxide Production
- Vascular Alterations
- Systemic Thrombotic Microangiopathy
- Capillary Rarefaction

Rao VU et al. JACC 2021; 77(21)
*Consider β-blockers if indication e.g. HF or CAD
### Recommended threshold for asymptomatic hypertension treatment in different clinical scenarios

<table>
<thead>
<tr>
<th>Home BP mmHg</th>
<th>CS</th>
<th>Curable cancer during treatment</th>
<th>Metastatic cancer Prognosis &gt;3 years</th>
<th>Metastatic cancer Prognosis 1–3 years</th>
<th>Metastatic cancer Prognosis &lt;1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>160+</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>140–159</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Consider treatment</td>
<td>May treat</td>
</tr>
<tr>
<td>135–139</td>
<td>Treat</td>
<td>May treat</td>
<td>Consider treatment</td>
<td>May treat</td>
<td>None</td>
</tr>
<tr>
<td>130–134</td>
<td>May treat</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>&lt;130</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

2022 ESC Guidelines on cardio-oncology
**FIGURE 2** Algorithm for QT-Interval Monitoring in Patients Receiving Oral Antineoplastic Agents

- **QTc increase >60 ms from baseline**
  - Female: QTc >480 ms
  - Male: QTc >470 ms
- **Manually measure QT and use Fridericia Correction Formula**
- **Correct for conduction abnormalities and/or arrhythmia**
- **Correct electrolytes (K >4.0 mmol/l; Mag >2.0 mEq/l)**
- **Eliminate other QT prolonging medications**
- **Consider alternative cancer therapy**

If baseline QT interval is prolonged, manual measurement and Fridericia correction should be completed. If QT increases by more than 60 ms from baseline to a level beyond 480 ms for females and 470 ms for males, QT should be corrected for conduction abnormalities/arrhythmias, electrolytes addressed, and concomitant QT-prolonging medications changed before proceeding with oral chemotherapy.

Rao VU et al. JACC 2021; 77(21)
Nilotinib has been associated with AS.
Case 2: CML follow-up

- Peripheral arterial disease → angioplasty and stent, statin
- Progressive AS → TAVR
- HFpEF → diuretics
- Hypertension → ACEi, beta blocker
- Continue bosutinib, avoid nilotinib and ponatinib
Many TKI are multitargeted with on- and off-target risk for cardiotoxicity

Wide spectrum of CV risk that varies by TKI; Even within a class, differences by specific drug

Treat HTN with ACEi and CCB

Be vigilant of other cardiovascular effects such as QT prolongation, HF, AF, vascular effects
Which of the following is true about ponatinib?

A. Significant hypertension is uncommon
B. Ponatinib has a safer CV side effect profile compared to imatinib
C. Arterial vascular disease is a potential side effect
D. Ponatinib increases QTc significantly
“There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.”

- Donald Rumsfeld
Immunotherapy and cardiovascular risk

Stein-Merlob et al. Heart 2020. 107(21)
2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)

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Opportunities to learn more cardio-oncology

• UW/SCCA/Fred Hutch/Seattle Children’s Cardio-oncology Symposium, led by Dr. Eric Chow – Seattle, **May 2023**

• American College of Cardiology Cardio-oncology Meeting – Washington D.C. + virtual option, **April 2023**