Cardio-Oncology and Breast Cancer

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Medstar Union Memorial Hospital and Good Samaritan Hospital
Medstar Medical Group

2019 Breast Cancer Symposium
Objectives

• Breast cancer treatment and cardiac dysfunction
  - Cardiotoxic therapies
  - Primary prevention of cardiac toxicity
  - Strain imaging

• Clinical Standards and guidelines

• Cardio-Oncology program
Scope of Need

- Estimated 3 million breast cancer (BC) survivors in the USA
- Shared common risk factors
- BC outcomes can be affected by preexisting cardiovascular disease (CVD)
- Some BC therapies associated with CV toxicities

Circulation. 2018;137(8):e30–66
Cumulative Leading Causes of Death by Time Since Breast Cancer Diagnosis

# Drugs with Potential Cardiovascular Toxicity

## Cardiotoxicity Incidence

<table>
<thead>
<tr>
<th>Chemotherapeutic Agent</th>
<th>Cardiotoxicity Incidence</th>
<th>Manifestations</th>
<th>Oncological Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>3%–26%</td>
<td>Myopericarditis, cardiac arrhythmia, ECG abnormalities</td>
<td>Acute myeloid leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, Hodgkin and non-Hodgkin lymphoma, kaposi sarcoma, systemic lupus erythematosus, breast cancer, brain cancer, Ewing sarcoma, transitional cell bladder cancer, multiple myeloma, gastric cancer, prostate cancer, lung cancer, neuropalstomatia</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>0.0%–3.3%</td>
<td>Cardiac arrhythmia, ECG abnormalities, arterial embolism</td>
<td>Breast cancer, myocardial ischemic</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>5%–18%</td>
<td>ECG abnormalities</td>
<td>Acute myeloid leukemia, acute myelogenous leukemia, multiple myeloma, gastric cancer, colon cancer, lung cancer, breast cancer, leukemia, lymphoma, myelodysplastic syndrome</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>0.2%–30.0%</td>
<td>Cardiac arrhythmia, ECG abnormalities, myocardial ischemia</td>
<td>Acute nonlymphocytic leukemia, prostate cancer (multiple sites)</td>
</tr>
<tr>
<td>Alkylation agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>7%–28%</td>
<td>Pericarditis/myopericarditis, cardiac tamponade, arrhythmia</td>
<td>Bone marrow transplant, bladder cancer, lung cancer, sarcoma, oral cancer, myelodysplastic syndromes, chronic myelogenous leukemia</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>17%</td>
<td>Arthrophy, cardiac arrest, myocardial hemorrhage, myocardial infarction</td>
<td>Testicular cancer, cervical cancer, Hodgkin and non-Hodgkin lymphoma, Ewing sarcoma, osteosarcoma, soft tissue sarcoma</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>10%</td>
<td>Rare</td>
<td>Stomach or pancreas adenocarcinoma, anal cancer, bladder cancer</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>21%</td>
<td>Arthrophy, hyperintensity, hyperperfusion, pericardial effusion</td>
<td>Acute lymphocytic leukemia</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>2%–20%</td>
<td>Coronary vasospasm, myocardial ischemia and infarction, arrhythmias, ECG changes including ventricular ectopy, hyperperfusion</td>
<td>Advanced colon cancer, anal cancer, gastrointestinal cancers, pancreatic cancers, hepatobiliary cancers, breast cancer, bladder cancer, head and neck cancers, as a radiation sensitizer in several tumors</td>
</tr>
<tr>
<td>Capetitabine</td>
<td>2%–7%</td>
<td>Coronary vasospasm, myocardial ischemia and infarction, arrhythmias, ECG changes, thrombosis</td>
<td>Breast cancer, advanced colon cancer, anal cancer, gastrointestinal cancers, pancreatic cancer, hepatobiliary cancers</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Undetermined</td>
<td>Pericarditis, chest pain (including angina)</td>
<td>Hodgkin and non-Hodgkin lymphoma, acute leukemia (myeloid and lymphoid)</td>
</tr>
<tr>
<td>Platinum agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Rare</td>
<td>Arterial vasospasm, arrhythmia</td>
<td>Lung cancer, bladder cancer, sarcoma, testicular cancer, ovarian cancer, head and neck cancer, metastatic breast cancer, cancer of unknown origin, esophageal cancer</td>
</tr>
<tr>
<td>Antimicrotubules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>25%</td>
<td>Myocardial ischemia and infarction, arrhythmia</td>
<td>Acute lymphocytic leukemia, central nervous system tumors, Hodgkin and non-Hodgkin lymphoma, multiple myeloma, Ewing sarcoma, ovarian cancer, small cell lung cancer, thymoma</td>
</tr>
<tr>
<td>Monoclonal antibody-based tyrosine kinase inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1.7%–3.0%</td>
<td>Arterial and venous thromboembolism</td>
<td>Renal cancer, colorectal cancer, lung cancer</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>2%–38%</td>
<td>Arthritis, venous thrombosis</td>
<td>HER2+ breast cancer, HER2+ endocrine resistant breast cancer</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>3%–7%</td>
<td>Arthritis</td>
<td>HER2+ breast cancer</td>
</tr>
<tr>
<td>Alimizumab</td>
<td>Rare</td>
<td>Arthritis</td>
<td>Chronic lymphocytic leukemia, cutaneous T-cell lymphoma, bone marrow transplant</td>
</tr>
</tbody>
</table>

## Cardiotoxicity Incidence

<table>
<thead>
<tr>
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<th>Cardiotoxicity Incidence</th>
<th>Manifestations</th>
<th>Oncological Use</th>
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</thead>
<tbody>
<tr>
<td>Small-molecule tyrosine kinase inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>2%–4%</td>
<td>Pericardial effusion, hypertension, arrhythmia, ECG changes</td>
<td>Philadelphia chromosome-positive chronic myeloid leukemia and acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>Imatinib</td>
<td>0.5%–1.7%</td>
<td>Pericardial effusion and tamponade, arrhythmia</td>
<td>Philadelphia chromosome-positive chronic myeloid leukemia and acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1.5%–2.2%</td>
<td>QTc-interval prolongation, myocardial ischemia (Pimelatil genome)</td>
<td>HER2+ breast cancer</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>3%–10%</td>
<td>Arterial and venous thrombus, aortic dissection, ECG changes</td>
<td>Renal cell cancer, pancreatic neuroendocrine tumors, gastrointestinal stromal tumors</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>4%–28%</td>
<td>Thrombosis, coronary vasospasm, myocardial ischemia/infarction</td>
<td>Renal cell cancer, hepatocellular carcinoma, differentiated thyroid carcinoma</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>7%–13%</td>
<td>Thrombosis, myocardial ischemia/infarction, blood clots, ECG changes</td>
<td>Renal cell cancer, soft tissue sarcoma</td>
</tr>
<tr>
<td>Immune checkpoint inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Multiple myeloma, mantle cell lymphoma</td>
</tr>
<tr>
<td>CTLA4 Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>2%–5%</td>
<td>Non-small cell lung cancer</td>
<td>Multiple myeloma, mantle cell lymphoma</td>
</tr>
<tr>
<td>PD-1 inhibitors</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Multiple myeloma, mantle cell lymphoma</td>
</tr>
<tr>
<td>Misflielins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>6%</td>
<td>Pericardial effusion</td>
<td>Multiple myeloma, chronic lymphocytic leukemia, cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>Pembrolizum</td>
<td>3%–10%</td>
<td>Myocardial ischemia and infarction, arrhythmia</td>
<td>Hairy cell lymphoma, chronic lymphocytic leukemia, cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>Pembrolizum</td>
<td>25%</td>
<td>Myocardial ischemia and infarction, ECG changes, sudden cardiac death</td>
<td>Metastatic melanoma, renal cell carcinoma</td>
</tr>
<tr>
<td>Pembrolizum</td>
<td>1.0%–6.8%</td>
<td>Myocardial ischemia/infarction, stroke</td>
<td>Metastatic colorectal cancer</td>
</tr>
</tbody>
</table>

JACC 2018;72:202-27
Drugs in Breast Cancer with Cardiovascular Toxicity Potential

• Chemotherapy
  • Anthracyclines (doxorubicin, epirubicin)
  • Pyrimidine analogues (5-FU, capecitabine)
  • Alkylating agents (cyclophosphamide, cisplatin)
  • Anti-microtubule (paclitaxel, docetaxel)

• Targeted/Biologic Rx
  • Anti-HER2 (trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib)
  • CDK 4/6 inhibitors (palbociclib and ribociclib)

Chang HM, Yeh ETH et al. JACC 2017:2536
Slide courtesy Dr Ana Barac
# Chemotherapy Induced LV Dysfunction

<table>
<thead>
<tr>
<th>Drug</th>
<th>HF incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>3-26%</td>
</tr>
<tr>
<td>Cytoxan</td>
<td>7-28%</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>2-28%</td>
</tr>
</tbody>
</table>

JACC 2018;72:202-27
Mechanism of Anthracycline Cardiotoxicity

- Reactive Oxygen Species and oxidative stress
- Iron accumulation
- Topoisomerase 2:
  - Two types: Top 2-alpha and Top 2-beta
  - Top 2 beta unwinds DNA strands during DNA replication, transcription or recombination
  - Top2 inhibition by anthracycline causes double-stranded DNA breaks and activation of apoptosis
- Toxicity can be acute, early or late

**Radiation Cardiotoxicity**

- Survivors have 2 to 6 x increased risk of radiation induced heart disease

- Contemporary techniques minimize cardiac exposure

- Proton therapy further minimizes radiation dose to the heart. RADCOMP trial ongoing.

Curr Treat Options Oncol. 2019 May 9;20(6):51
Front Oncol. 2015; 5: 39
Strain Imaging

- Normal values of LV global longitudinal strain: −15.9% to −22.1%

- Negishi et al.; change in GLS at 6 months of 11%; strongest predictor of cardiotoxicity among trastuzumab-treated patients

- ASE guidelines; relative decrease in GLS of >15% likely to reflect a clinically significant change in LV function

Guidelines
Clinical Practice Recommendations for Prevention and Monitoring of Cardiac Dysfunction

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)
ASCO 2016 Guidelines Clinical Questions

Which cancer patients are at increased risk for developing cardiac dysfunction?
Recommendation 1

Cancer diagnosis

Which preventative strategies minimize risk before initiation of therapy?
Recommendation 2

Start of treatment

What strategies minimize risk during potentially cardiotoxic therapy?
Recommendation 3

End of treatment

What are the preferred surveillance / monitoring approaches during treatment in patients at risk for cardiac dysfunction?
Recommendation 4

What are the preferred surveillance / monitoring approaches after treatment in patients at risk for cardiac dysfunction?
Recommendation 5

Armenian S. JCO 2017: 35:893
Question # 1: Who is at Increased Risk?

- High dose anthracycline (e.g. ≥250 mg/m² doxorubicin, ≥600 mg/m² epirubicin)
- High dose (≥30 Gy) radiotherapy where the heart is in the treatment field
- Lower dose anthracycline (e.g. <250 mg/m² doxorubicin) in combination with lower dose radiotherapy (<30 Gy) where the heart is in the treatment field
Question # 1: Who is at Increased Risk?

- Treatment with lower dose anthracycline (e.g. <250 mg/m² doxorubicin) or trastuzumab alone, and presence of any of the following risk factors:
  - Multiple (≥2) CV risk factors: smoking, hypertension, diabetes, dyslipidemia, obesity
  - Older (≥60 years) age at cancer treatment
  - Compromised cardiac function (e.g. borderline low LVEF [50-55%], history of myocardial infarction, ≥moderate valvular heart disease)

- Treatment with lower dose anthracycline (e.g. <250 mg/m² doxorubicin) followed by trastuzumab (sequential therapy)
Question # 1: Who is at Increased Risk?

No Determination of Risk

- Lower dose anthracycline (e.g. <250 mg/m² doxorubicin, <600 mg/m² epirubicin) or trastuzumab alone, and no additional risk factors
- Lower dose radiotherapy (<30 Gy) where the heart is in the treatment field, and no additional cardiotoxic therapeutic exposures or risk factors
- Kinase inhibitors
- *(Evidence-based; Evidence quality: Low)*
Question # 2: Preventive Strategies Prior to Treatment

Recommendation 2

Which preventative strategies minimize risk \textit{prior to} initiation of therapy?

<table>
<thead>
<tr>
<th>Cancer diagnosis</th>
<th>Start of treatment</th>
<th>End of treatment</th>
</tr>
</thead>
</table>

Recommendation 2.1

\textbf{Avoid or minimize the use of potentially cardiotoxic therapies if established alternatives exist that would not compromise cancer-specific outcomes. (Consensus-based; Benefits outweigh harms; Strength of Recommendation: Strong).}

Recommendation 2.2

\textbf{Comprehensive assessment in cancer patients that includes an H&P, screening for cardiovascular disease risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking), and an echocardiogram prior to initiation of potentially cardiotoxic therapies. (Evidence and consensus-based; Benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong).}
Question # 3: Preventive Strategies during Treatment

• Recommendation 3.1
  Clinicians should screen for and actively manage modifiable cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia, obesity) in all patients receiving potentially cardiotoxic treatments.

• (Informal consensus and evidence-based; Benefits outweigh harms; Evidence quality: Insufficient; Strength of Recommendation: Moderate)

• Recommendation 3.2
  Clinicians may incorporate a number of strategies, including use of the cardioprotectant dexrazoxane, or continuous infusion, or liposomal formulation of doxorubicin for prevention of cardiotoxicity in patients planning to receive high-dose (e.g. ≥250 mg/m2 doxorubicin) anthracyclines.
Primary Prevention

Recommendation 3.4

No definitive recommendations can be made on the use of the following potential cardioprotectants during anthracycline administration:

- Statins in patients without dyslipidemia
- Carnitine, L-acetylcysteine, Coenzyme Q, Amifostine, or Phenethylamines
- Bblockers and ACEI in normotensive patients
- Evidence-based; Relative balance of benefits and harms; Evidence quality: Low.

Several studies have evaluated the efficacy of prophylactic use of beta blockers and renin-angiotensin aldosterone system blockers to prevent LV systolic dysfunction associated with adjuvant anthracycline and/or trastuzumab therapy in patients with early breast cancer.
## Primary Prevention Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Details</th>
<th>EF on ECHO</th>
<th>EF on CMR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRADA</strong></td>
<td>(N =130) Rx with Epirubicin, 22% also received Trastuzumab 2x2 Metoprolol and Candesartan</td>
<td>EF decline attenuated in Candesartan Arm (2-3%)</td>
<td>EF on CMR</td>
</tr>
<tr>
<td><strong>MANTICORE</strong></td>
<td>(N =94) Rx with Trastuzumab, 12-33% also received AC 1:1:1 bisoprolol, perindopril, placebo</td>
<td>EF decline attenuated in Bisoprolol arm (4%)</td>
<td>LVEDVi on CMR</td>
</tr>
<tr>
<td><strong>CECCY</strong></td>
<td>(N =200) Rx Doxorubicin 1:1 Carvedilol and Placebo</td>
<td>No significant difference in change in EF</td>
<td>EF on ECHO</td>
</tr>
<tr>
<td><strong>Lisinopril or Carvedilol</strong></td>
<td>(N =468) Rx with Trastuzumab, 40% also received doxorubicin 1:1:1 Carvedilol, Lisinopril, placebo</td>
<td>No difference for Trastuzumab. Some benefit in AC arm</td>
<td>EF on ECHO</td>
</tr>
</tbody>
</table>
Statins

- N = 628
- Newly diagnosed with breast CA
- Treated with Anthracyclines
- Primary outcome: Incident HF hospitalization

J Am Coll Cardiol. 2012;60(23):2384–90
Pilot Study Evaluating the Cardiac **SAFEty** of **HER2 Targeted** therapy in Patients with HER2 Positive Breast Cancer and Reduced Left Ventricular Function

- Investigator-initiated, funded by Genentech, Inc.
- IND for trastuzumab, pertuzumab and TDM-1
- Inclusion Criteria:
  - Stage I-VI HER2+ breast cancer
  - LVEF 40-49%
  - No HF in the past 12 months

Slide courtesy Dr Ana Barac
SAFE HEaRt: Cardiac Medication Titration


Slide courtesy Dr Ana Barac
Completion of Planned Oncology Therapy Without

- **Asymptomatic LV dysfunction**
  - Decline in LVEF >10% and/or decrease to LVEF ≤35% *

- **Cardiac Event (CE)**
  - Symptomatic HF
  - Cardiac arrhythmia requiring intervention
  - MI
  - Sudden cardiac death or death due to MI, arrhythmia or HF

Breast Cancer Res Treat. 2019 Jun;175(3):595-603

Slide courtesy Dr Ana Barac
Question # 4: Preferred Surveillance/Monitoring Approaches DURING treatment in Patients at risk for Cardiac Dysfunction

• Routine Surveillance imaging may be during treatment in asymptomatic patients considered to be at increased risk of developing cardiac dysfunction. ECHO is the preferred m

• No recommendation can be made regarding continuation or discontinuation of therapy in individuals with evidence of cardiac dysfunction.

Armenian S. JCO 2017: 35:893
Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy (ASE/ EACVI)

Initiation of trastuzumab after regimen associated with Type I toxicity

Baseline evaluation of LVEF
3D (preferred) / 2D (consider contrast)
GLS, Troponin I

LVEF < 53%*
GLS < LLN**
+ Troponins
Cardiology consultation

LVEF > 53%
GLS > LLN**
-Tn I
F/U every 3 months during therapy, and 6 months later

* Consider confirmation with CMR.
** LLN = Lower limit of normal. Please refer to Table 5 for normal GLS values based on vendor, gender and age.
Medstar Cardio-Oncology Program

• Team approach - Partner with oncologists in managing this patient population before, during and after treatment

• Creating a streamlined process for referrals

• Involvement in survivorship; crafting a plan for patients post treatment

• Partnering with primary care doctors to manage cardiac complications that may develop
Cardio-Oncology Program Across Medstar

• **MedStar DC**
  Dr Ana Barac – director of Medstar Cardio-Oncology
  Dr Ian Chang
  Rachel Barish, NP

• **Medstar Baltimore**
  - Drs. Tolulope Agunbiade and Sri Padmanabhan
  - Drs. Albert Aboulafia and Yvonne Ottaviano

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Advancing the Cardiovascular Care of the Oncology Patient

FEBRUARY 14 – 16, 2020
The Ritz-Carlton
Washington, DC

COURSE DIRECTORS
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For more information visit
ACC.org/CVOncology
Thank you