Kettering Cancer Center
on the Kettering Medical Center campus
Opening January 2017
Calvert R. Busch MD, FACC

- Staff Cardiologist
- Southwest Cardiology/KPN
- No Financial Disclosures
Background

- Mid 1970’s Anthracycline caused decrease in LV ejection fraction
- Most toxicity in first year post Rx
- Toxicity from Anthracycline may not be evident for years or decades after exposure
  - As high as 8% of patients
  - May appear 10-20 years later
Cancer approx. 13% of total deaths in the world

In 2013, Breast, Lung, Colorectal Cancer accounted for 6-8 years of lost healthy life in US, UK, Australia

Cancer—curse of the developing world
The Emperor of All Maladies
A Biography of Cancer
Siddhartha Mukherjee

"A compulsively readable, surprisingly uplifting, and vivid tale. Thrilling."
—O. The Oprah Magazine
Currently, there are more than-

- 14 million cancer survivors in the United States
- By 2020, 20 million survivors are expected
- Cancer drugs not only kill cancer cells, but also cause collateral damage to healthy cells
Incidence of cardiovascular disease in the cancer patient is higher than in the general population
Prevalence of Cardiovascular Diseases by Type of Malignancy

**Figure 1.** Prevalence of cardiovascular diseases by type of malignancy.
Abstract

The care for patients with cancer has advanced greatly over the past decades. A combination of earlier cancer diagnosis and greater use of traditional and new systemic treatments has decreased cancer-related mortality. Effective cancer therapies, however, can result in short- and long-term comorbidities that can decrease the net clinical gain by affecting quality of life and survival. In particular, cardiovascular complications of cancer treatments can have a profound effect of the health of patients with cancer and are more common among those with recognized or unrecognized underlying cardiovascular diseases. A new discipline termed cardiovascular-oncology has thus evolved to address the cardiovascular needs of patients with cancer and optimize their care in a multidisciplinary approach.
Cardiovascular - Oncology

- Integration of care to optimize the best outcome for the cancer patient
  - Concept is not new
  - **Goal** – Maximize survival of cancer patient, minimize adverse cardiac effect of therapy, and enhance Quality of Life.
Cardiovascular-Oncology – Why?

- Address Cardiovascular needs of the cancer patient
- Collaborative effort of multiple disciplines
  - Cardiology ↔ Oncology
  - Radiation oncology
  - Pharmacologist
  - Imaging specialists
    - Ultrasound, MR, PET, Nuclear
  - Nursing
  - Dieticians
  - Social Workers
  - Physiatrists
  - Spiritual
  - Alternative Therapies
Cancer and its therapy results in fatigue and frequently shortness of breath (for many reasons).

In this setting, there is a clear need to know if there is preexisting heart disease.

Post cancer therapy - there is need for long term continued observation and care.
It is important to recognize that all chemotherapy agents may have potential cardiotoxic effects.
<table>
<thead>
<tr>
<th>Heart Failure</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>+++</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>++</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>++</td>
</tr>
<tr>
<td>HER2 antagonists</td>
<td>+++</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>+</td>
</tr>
<tr>
<td>VEGF Inhibitors</td>
<td>+</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>+</td>
</tr>
<tr>
<td>Docetaxel*</td>
<td>+</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>+</td>
</tr>
<tr>
<td>Ischemia</td>
<td>++</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>++</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>+</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>+</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>+</td>
</tr>
<tr>
<td>Androgen Deprivation Therapy</td>
<td>++</td>
</tr>
<tr>
<td>Hypertension</td>
<td>++</td>
</tr>
<tr>
<td>VEGF inhibitors</td>
<td>+++</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>+++</td>
</tr>
<tr>
<td>Interferon-alpha</td>
<td>++</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td></td>
</tr>
<tr>
<td>Dasatinib</td>
<td>+</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>++</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>+</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>+</td>
</tr>
<tr>
<td>Arterial Thrombotic Events</td>
<td>++</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>+</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>++</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QT Prolongation</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic Trioxide</td>
<td>+++</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>+</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>+</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>+</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>+</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>+</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>++</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>++</td>
</tr>
<tr>
<td>Melphalan</td>
<td>++</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>+++</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>+++</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>++</td>
</tr>
<tr>
<td>VEGF Inhibitors</td>
<td>+++</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>+</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>++</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>+++</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>+</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>++</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>+</td>
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<tr>
<td>Edema</td>
<td>++</td>
</tr>
<tr>
<td>Imatinib</td>
<td>+++</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>++</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>++</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>++</td>
</tr>
<tr>
<td>Pericardial Effusion</td>
<td>+</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>+</td>
</tr>
</tbody>
</table>

Table 1
Cardiotoxicity Associated With Various Cancer Therapy Agents

Severity is denoted by + signs.

*In conjunction with anthracyclines.

HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor.

ASE Definition

- **CTRCD – Cancer Therapeutics-Related Cardiac Dysfunction**
  - Decrease in LVEF$_X$ >10% to value <53%

- **Reversibility**
  - Reversible to within 5% of baseline
  - Partially reversible
    - Improve by >10% points but remaining >5% points below baseline

- **Irreversible**
  - Improved by <10% points and remaining >5% points below baseline
Cardiotoxicity – National Cancer Institute

- Chemo/Radiation may have adverse effects on heart and/or vascular system
- Cancer patients are surviving longer—important to recognize late cardiotoxicity
  - Direct effect on Cardiac Myocytes → CHF
  - Indirect effects
    - Hypertension/systemic/pulmonary effects
    - Arterial/venous vascular effects
      - Coronary artery disease
      - Thromboembolism
    - Arrhythmias-conduction abnormalities
    - Valvular disease
    - Pericardial disease
• May cause changes in drug metabolism
  ○ Calcium channel blockers may increase intracellular levels of cardiotoxic therapy
    ▪ e.g. Verapamil, Diltiazem
Cardiovascular Toxicity
Any disorder (abnormality) of heart or circulatory system that occur during or after anti cancer therapy.
Collateral Damage of Cancer Therapy

- Cardiac
- Vascular
- INCREASED RISK OF DEVELOPING NEW CANCER
Cardiotoxicity in Real World

Unfortunately-

- Potential cardiotoxicity effects not recognized until released into the “real world of chemotherapy”

- Cancer trials exclude cardiac patients
Cardiovascular - Oncology – Goals

- Recognize cancer patient at increase risk to develop cardiac toxicity
- Prevent adverse effects
  - Early recognition
  - Careful monitoring
  - Provide protective medication
  - Manage, minimize toxicity
- ENHANCE QUALITY OF LIFE
- CANCER PATIENT SHOULD NOT BECOME HEART FAILURE PATIENT

Common Access Point – Cancer Center
Heart failure symptoms/not always obvious:

- Signs of Heart Failure
  - Tachycardia
  - Edema
  - S\textsubscript{3} Gallop

Once the ejection fraction is reduced, there already is advanced disease.
### Characteristics of Type I and II CTRCD

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic agent</strong></td>
<td>Doxorubicin</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td><strong>Clinical course and typical response to antiremodeling therapy (β-Blockers, ACE inhibitors)</strong></td>
<td>May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress</td>
<td>High likelihood of recovery (to or near baseline cardiac status) in 2-4 months after interruption (reversible)</td>
</tr>
<tr>
<td><strong>Dose effects</strong></td>
<td>Cumulative, dose related</td>
<td>Not dose related</td>
</tr>
<tr>
<td><strong>Effects of rechallenge</strong></td>
<td>High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death</td>
<td>Increasing evidence for the relative safety of rechallenge (additional data needed)</td>
</tr>
<tr>
<td><strong>Ultrastructure</strong></td>
<td>Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)</td>
<td>No apparent ultra structural abnormalities (though not thoroughly studied)</td>
</tr>
</tbody>
</table>
Type 1 - Cardiotoxicity

- **Anthracyclines (doxorubicin, epirubicin)**
  - DNA Fragmentation
  - Release $O_2$ Free Radicals
- **Dose Dependent**
  - $>550 \text{ mg/m}^2$ – 25% risk
  - Risk factors for toxicity: age, history of heart disease, female gender, radiation therapy, other chemo agents, decrease ejection fraction $<50$
- **Risk increased if given with Herceptin (trastuzumab)**
• Anthracyclines
  ○ Effective anticancer therapy discovered 50 years ago (Dr. Paul Ehrlich “Chemotherapy”)
  ○ Still play important role in current therapies
    ▪ Risk for CHF up to $400\text{mgm/m}^2 \rightarrow 5\%$
Type II - Cardiotoxicity

- **Trastuzumab (Herceptin)**
  - Rx: HER-2 Positive Metastatic Breast Cancer
  - Inhibits HER-2 Receptor
  - Severe heart failure up to 4%
  - Symptomatic heart failure up to 5%
  - Asymptomatic decrease cardiac function 14%
    - Usually reversible
    - May tolerate reintroduction after recovery

Those who fail to recover = previously exposed to Anthracycline
Recovery (6-12 months)?
Other HER2 Antagonists

- Lapatinib (Tykerb)
- Pertuzumab (Perjeta)
- T-DMI (Kadcyla)
- ? May have less cardiotoxicity
Cardiac Ischemia

- Coronary Vascular Endothelial Dysfunction
- Coronary Vasospasm (etoposide)
- Vaso occlusive complication (vinblastine)
- Atherogenic effects of Chemo
Arrhythmia

- Direct toxicity
- Metabolic changes
  - Interleukin 2 (Proleukin)
    - Increase vascular permeability
    - Volume depletion
  - Repolarization abnormality (arsenic-increase QT 40%)
  - Change in hepatic metabolism
  - Drug – Drug interaction (imatinib)
Pericarditis

- Inflammation / myopericarditis
  - Cyclophosphamide, cytarabine, bleomycin
Thrombo Embolic Complications

- Hypercoagulable state and vascular injury
  - Thalidomide
- ASA?
- CANCER PATIENTS “CLOT AND BLEED”!
Radiation Therapy

- Improves outcomes in a variety of malignancies
- May have serious side effects
- “Recent” changes in radiation therapy have decreased changes secondary to radiation
Radiation Therapy

- Late effects usually second to third decade Affects 10-30% by 10 years post therapy
- Children as young as 12
  - Sudden death secondary to left main stenosis post therapy
Radiation Therapy

- Valvular fibrotic change
- Endothelial damage → CAD
- Myocardial fibrosis systolic / diastolic dysfunction
- Pericarditis / Constrictive
- Additive effect with chemo
Radiation Therapy - Pathophysiology

- Inflammation, DNA Disruption, Endothelial Dysfunction, Fibrosis, Small Vessel Occlusion
- Synergistic effect with Chemo
Radiation Effects on the Heart/Vessels

- CAD / Vascular
- Valvular (Mitral & Aortic)
- Myocardial Disease
  - Cardiomyopathy
    - Systolic
    - HFPEF
- Pericardial
- Conduction System Disease
CAD - Radiation Effects

- **Ostial Stenosis**
  - Left main
  - RCA
  - LAD

- **Vascular → Carotid, subclavian internal mammary!**

- **Valvular**
  - Aortic / Mitral
  - Regurgitation early (Retraction)
  - Stenosis, calcification (Late)
    - 25% → Ca++ Aortic – Mitral Curtain
Pericardial

- Acute (weeks)
- Chronic
  - 5-10 years - constrictive, effusive constrictive
- Conduction System
  - RBBB LBBB
    - Pacemaker
  - Ventricular ectopy
  - Autonomic Dysfunction
    - ? Denervation
    - Persistent tachycardia
Post Radiotherapy Evaluation

- Not Clear
- Baseline **Stress Echo** at 5 years?
  - Or after age of 30
- Now pregnant
  - Assess during 2\textsuperscript{nd} trimester
- Annual EKG
  - Conduction Disease
  - Athletic Screening
  - ? MR, ? Ca Score
- Caroid ultrasound/cerebro vascular disease
- Exam/Bruit?
Who Should Be Evaluated?

- **Team Approach**
  - Evaluation of previously treated patients
  - Pre-cancer therapy
  - Ongoing evaluation during therapy
  - Post therapy – F/U – Decades
  - To include specialized therapies for complications beyond CHF, (i.e. arrhythmias, end stage disease)
  - Metastatic, invasive disease
  - Preop surgical cancer patient?
  - (inpatient consultation)
Guidelines-Don’t Exist

- Consensus Statements
  - ASE
  - European Society of Cardiology
  - Cancer Society
  - SCAI
- Nuclear Medical Society
- No guidelines for monitoring more than 70 agents currently available
- No guidelines for long term surveillance post cancer treatment
Evaluation to Include

- Detailed clinical cardiovascular evaluation ("Risk Score")
- EKG, Chest X-ray
- Baseline Echo, Serial Echo, EFX (Preferably 3D), 2D (Biplane Simpsons) contrast, wall motion score index
- Strain – Detect Subclinical LV systolic dysfunction
Cardiac Ultrasound

- Preferably 3D if available
- Important to calculate $\text{LVEF}_x$
- Consecutive studies, preferably same:
  - Lab
  - Personnel
  - Vendor
Diastolic parameters are currently not recommended in predicting LV dysfunction (they are not good predictors of future systolic dysfunction)

Plana
European Assoc. Cardiovascular Imaging-2014

Myocardial deformation is best for early detection of cardiotoxicity

Thavendiranathan
JACC -2014
Myocardial Deformation (Strain)

- Robust method to measure myocardial function
- Strain = dimension less index reflecting deformation of myocardium during one cycle length
  - It is measured as a percentage of its initial length
  - Prognosticates decrease in LVEF$_X$
LV Strain

Peak Systolic Strain
HR (Avg.) = 59 bpm
EDV (Bi-Plane) = 137.2 ml
ESV (Bi-Plane) = 45.6 ml
EF (Bi-Plane) = 66.8%
Time (ms) = 51.1 ms

AP3 L Strain = -24.7%
AP4 L Strain = -25.0%
AP2 L Strain = -28.0%
Global L Strain = -25.9%

Enter AVC time in Cardiac Cycles.
AP4 L Strain = -25.0%
## Risk Assessment

<table>
<thead>
<tr>
<th>Medication-related risk</th>
<th>Patient-related risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High (risk score 4):</strong></td>
<td>Cardiomyopathy or heart failure</td>
</tr>
<tr>
<td>Anthracyclines, Cyclophosphamide, Ifosfamide, Clofarabine, Herceptin</td>
<td>CAD or equivalent (incl. PAD)</td>
</tr>
<tr>
<td><strong>Intermediate (risk score 2):</strong></td>
<td>HTN</td>
</tr>
<tr>
<td>Docetaxel, Pertuzumab, Sunitinib, Sorafenib</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td><strong>Low (risk score 1)</strong></td>
<td>Prior or concurrent anthracycline</td>
</tr>
<tr>
<td>Bevacizumab, Dasatinib, Imatinib, Lapatinib</td>
<td>Prior or concurrent chest radiation</td>
</tr>
<tr>
<td><strong>Rare (risk score 0)</strong></td>
<td>Age &lt;15 or &gt;65 years</td>
</tr>
<tr>
<td>For example, Etoposide, Tituximab, Thalidomide</td>
<td>Female gender</td>
</tr>
</tbody>
</table>

### Overall risk by Cardiotoxicity Risk Score (CRS)
(Risk categories by drug-related risk score plus number of patient-related risk factors: CRS>6: very high, 5-6: high, 3-4: intermediate, 1-2: low, 0: very low)
Monitoring Recommendations

- **Very high cardiotoxicity risk:** TTE with strain before every (other) cycle, end, 3-6 months and 1 year, optional ECG, cTn with TTE during chemotherapy
- **High Cardiotoxicity risk:** TTE with strain every 3 cycles, end, 3-6 months and 1 year after chemotherapy, optional ECG, cTn with TTE during chemotherapy
- **Intermediate cardiotoxicity risk:** TTE with strain, mid-term, end and 3-6 months after chemotherapy, optional ECG, cTn mid-term of chemotherapy
- **Low cardiotoxicity risk:** Optional TTE with strain and/or ECG, cTn at the end of chemotherapy
- **Very low cardiotoxicity risk:** None
  - Mayo Clinic
    - ?? Over test
Management Recommendations

- **Very high cardiotoxicity risk**: Initiate ACE-I/ARB, Carvedilol, and statins, starting at lowest dose and start chemotherapy 1 week prior to initiation to allow steady state, up-titrate as tolerated
- **High cardiotoxicity risk**: Initiate ACE-I/ARB, Carvedilol, and/or statins
- **Intermediate cardiotoxicity risk**: Discuss risk and benefit of medications
- **Low cardiotoxicity risk**: None, monitoring only
- **Very low cardiotoxicity risk**: None, monitoring only
**Most Commonly Used Chemotherapeutic Agents with Cardiotoxicity Potential**

<table>
<thead>
<tr>
<th>Chemotherapeutic class and agents</th>
<th>Cardiomyopathy incidence</th>
<th>Other types of cardiovascular toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines-Doxorubicin</td>
<td>3% - 26%</td>
<td>Myopericarditis, cardiac arrhythmias, ECG abnormalities</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>0.9%-3.3%</td>
<td>Cardiac arrhythmias, ECG abnormalities</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>5%-18%</td>
<td>ECG abnormalities</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>0.2%-30%</td>
<td>Cardiac arrhythmias, ECG abnormalities, myocardial ischemia, hypertension</td>
</tr>
<tr>
<td>Alkylating agents - Cyclophosphamide (high dose)</td>
<td>7%-28%</td>
<td>Peri-/myocarditis, cardiac tamponade, arrhythmias</td>
</tr>
<tr>
<td>Ifofamide</td>
<td>17%</td>
<td>Arrhythmias, cardiac arrest, myocardial hemorrhage, myocardial infarction</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Rare</td>
<td>Endomyocardial fibrosis, pericardial effusion and tamponade, ECG changes, chest pain, hyper-/hypotension, thrombosis, arrhythmias</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>2%-20%</td>
<td>Coronary vasospasm, myocardial ischemia and infarction, arrhythmias, ECG changes, including ventricular ectopy, hypotension</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2%-7%</td>
<td>Coronary vasospasm, myocardial ischemia and infarction, arrhythmias, ECG changes, thrombosis</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Undefined</td>
<td>Pericarditis, chest pain (including angina)</td>
</tr>
<tr>
<td>Platinum agents Cisplatin</td>
<td>Rare</td>
<td>Arterial vasospasm, cardiac/cerebral/mesenteric/limb ischemia, hypo-/hypertension, arrhythmias</td>
</tr>
<tr>
<td>Antimicrotubule agents - Viscristine</td>
<td>25%</td>
<td>Hyper-/hypotension, myocardial ischemia and infarction, arrhythmias</td>
</tr>
</tbody>
</table>
# Monoclonal anti-body based tyrosine kinase inhibitors

<table>
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<th>Chemotherapeutic class and agents</th>
<th>Cardiomyopathy incidence</th>
<th>Other types of cardiovascular toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>1.7%-3%</td>
<td>Hypertension, arterial and venous thromboembolism</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>2%-28%</td>
<td>Hyper-/hypotension, arrhythmia, vascular thrombosis</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>3%-7%</td>
<td>Hypo-hypertension, arrhythmia</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Small-molecule tyrosine kinase inhibitors-Dasatinib</td>
<td>2%-4%</td>
<td>Pericardial effusion, hypertension, arrhythmia, QT interval prolongation</td>
</tr>
<tr>
<td>Imatinib mesylate</td>
<td>0.5%-1.7%</td>
<td>Pericardial effusion, and tamponade, anasarca, arrhythmias, hypertension, Raynaud disease</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1.5%-2.2%</td>
<td>QTc interval prolongation, myocardial ischemia (Prinzmetal angina)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>3%-15%</td>
<td>Hypertension, arterial and venous thrombosis, arrhythmias, aortic dissection, QTc prolongation</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>4%-28%</td>
<td>Hypertension, thrombosis, coronary vasospasm, myocardial ischemia/infarction</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>7%-13%</td>
<td>Hypertension, thrombosis, myocardial ischemia/infarction, bradycardia, QTc interval prolongation</td>
</tr>
<tr>
<td>Proteasome inhibitor-Bortezomib</td>
<td>2%-5%</td>
<td>Ischemia, bradycardia</td>
</tr>
<tr>
<td>Miscellaneous All-trans-retinoic acid</td>
<td>6%</td>
<td>Hypotension, pericardial effusion</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>3%-10%</td>
<td>Myocardial ischemia and infarction, acute arrhythmias</td>
</tr>
<tr>
<td>Interferon alpha-2b</td>
<td>25%</td>
<td>Hypotension, myocardial ischemia and infarction, ECG changes, sudden cardiac death</td>
</tr>
<tr>
<td>Afibercept</td>
<td>1%-6.8%</td>
<td>Hypertension, myocardial ischemia/infarction stroke</td>
</tr>
</tbody>
</table>
Strain Studies

- Sensitive measure of change in myocardial mechanics
  - Detect subclinical LV systolic dysfunction
- Some variation Men and Women
- Normal
  - Men 20.7 ± 2
  - Women 22.1 ± 1.8
- Tend to decrease with age
- Inter-vendor and software variability
• Abnormal
  o Reduction <8% - not significant
  o Reduction >15% clinically likely to be significant

• Limitations of Strain
  o Quality of image
  o Loading conditions
  o Lack of long term clinical trials
  o ? reproducibility
  o Vendor, software specific
Additional Studies May Include

- Evaluate valvular disease - TTE
- TEE may be necessary
- Pericardial evaluation
  - MR
  - CT
- Vascular disease
  - US carotids
  - ABIs
Stress Echocardiography

- Evaluate subclinical LV dysfunction
- Evaluate contractile reserve (patient with known CTRCD)
  - Dobutamine stress
- Treatments causing ischemia
  - Fluorouracil, Bevacizumab, Sorafenib, Sunitinib
Biomarkers

- Early identification and monitoring of CTRCD
- Troponin
  - Sensitive for myocardial injury
  - May identify early injury in patients receiving newer targeted Rx (Anti-VEGF, tyrosine kinase inhibitors)
  - Normalization with β Blocker, ASA, ACE, may allow rechallenge with drug
  - ? When to draw, how often, normal cut off
BNP (Brain Natriuretic Peptide)
- Reflect elevated filling pressures
- Not consistent in identifying CTRCD?
Kinase Inhibition

- Monoclonal Antibody
- Small molecule kinase inhibitors
- VEGF inhibitors (signal pathways)
- TKIs with anti VEGF activity
Monoclonal Antibody

- **Trastuzumab**
  - Targets HER2 receptor
  - Symptomatic CHF 2-4%
  - Asymptomatic dysfunction 3-19%
  - 1/3 may have persistent cardiac dysfunction
VEGF Signaling Pathway Inhibitor

- Bevacizumab
- Sunitinib
- Sorafenib
- Ponatinib

- Increase BP 25-60% of patients
- Increase thrombotic vascular events
  - 10% risk of asymptomatic cardiac dysfunction
  - High incidence of thrombotic microangiopathy on renal biopsy (similar changes in preclampsia)
Small Molecule Inhibitors

- Imatinib
- Dasatinib (develop pulmonary hypertension)
- Nilotinib
- Ponatinib
  - Cardiac events, CNS, PAD (increased risk with associated cardiac risk factors)
- Ibrutinib
  - 3% incidence Atrial Fib
Immune Modulating Drugs

- Thalidomide, Lenalidomide
  - Risk arterial (MI, CVA) events
Proteasome Inhibitor

- Carfilzomib
  - CHF, Venous Thromboembolic Disease, Hypertension
Check Point Inhibitor

- Autoimmune myocarditis reported
Cardiovascular Effects of Targeted Cancer Therapies

New England Journal of Medicine October 13, 2016 pg. 1465
ABCDE Approach (Prevention)

- **A**
  - Awareness
  - Assessment
  - Aspirin

- **B**
  - Blood Pressure Control

- **C**
  - Cholesterol lowering
  - Cigarette Cessation

- **D**
  - Diet
  - Chemo Dose
  - Diabetic Control

- **E**
  - Exercise
  - Echo Surveillance

Moslehi, NEJM Oct 2016
Stanford Protocol for Monitoring Targeted Rx

Baseline Assessment
- LVEF
- BNP
- BP Control

BP at every clinic visit
- home monitoring
  - SBP > 140
  - SBP > 90
  - Start Therapy

Repeat at 1 month and every 3 months on treatment
- 10% Fall in LVEF
- Increase BNP or 100% Increase over baseline

Screen for HF Symptoms
- Symptoms
  - CHF Clinic
Case Slide

- Case
Best Monitoring Approach Requires Further Research
Other Monitoring Modalities

- MUGA (Traditional, 1970’s - evaluate anthracycline toxicity)
  - Reproducible, serial testing
  - Disadvantage
    - Radiation exposure
  - No information re: Atrial size, valvular or pericardial disease
  - Maybe complementary to Echo
Other Monitoring Modalities

- **CMR**
  - Reference standard for LV, RV volume and function
  - Gold standard for myocardial viability
  - Detects decrease LV mass
  - Good correlation with Echo
  - Detect cardiac metastasis or invasion
If discontinuation of chemo therapy is being considered, and there is question of technical quality of Echo, then MR should be performed.

Earliest change maybe tissue edema.
• Annexin also shown to identify apoptosis on nuclear imaging – very early change
• Further study pending out of Canada

Posterboard Vancouver 10/2016
What should we do with our current knowledge base?

- Multidisciplinary approach requiring close collaboration between oncology and cardiology
- Baseline Assessment –
  - Every Patient? IDEAL
  - Risk score
  - Receiving Type 1 dose > 350mg/m² or combo Type I and II
• Prior exposure to chemotherapy/radiation
  o Identify cancer
  o Identify agent
  o Radiation chemo $R_x$ | How Much/Cancer Site

*HISTORY and CARDIOVASCULAR EXAM

- EKG
- Echo/3DEFx
  (if available)
- Stress Test (consider)
  + Strain

- $R_x$ Risk Factors
- Surveillance
Pre Therapy

Cancer Rx

Type 1

EKG  Trop  Echo*/3DEFx/LS

EFx < 53%
GLS < LLN

Troponins
Benefit Discussion

Risk Score

EFx < 240 mg/m²

If > 240
Evaluate before each cycle

LVEFx > 53%
GLS > LLN

Troponins

Reevaluate Completion of Rx

LVEFx ↓10% < 53%

CTRCD

Troponins

8% or GLS < 15%

Echo 6 mos.
Post Rx

Cont

Type 2

Echo/3D/EKG

EFx < 53%
GLS < LLN

Troponins

F/U q 3 mos.
During Rx

LVEFx > 53%
GLS > LLN

Troponins

Post Rx ???
Yearly

Veg F
F/U 1 mo.
And q 3 mos. while on Rx

*If suboptimal Echo → CMR
LLN – Define < 18%
3D / or 2D – Biplane Simpsons / Contrast

* Confirm CMR after each cycle
Type 2 Following Type 1

Baseline

LVEFx (3D) / 2D (Contrast)
GLS Troponin

LVEF < 53%
GLS < LLN ⊕ Troponin
Evaluate Risk
Benefit

LVEF > 53%
GLS ≥ LLN ⊗ Troponin
F/U q 3 months during Rx
6 months
Treatment Available

- ACE
- ARB
- \(\beta\) Blocker (carvedilol preferred)
- ASA?
- Statin
  - Aldosterone
  - Dexrazoxane
- Stem Cell?
  - Anthracycline Cardiomyopathy
- LVAD?
- Transplant?
• Ongoing multiple studies
  ○ MANTICORE, PRADA, SUCCOUR, ELEVATE
Follow Up Essential

- How long?
- Frequency?
- How long Cardioprotection?
  - ? 12 months if normalized

- But – Late Cardiotoxicity May Be Decades
Primary Prevention – Small Study Size

- Relative risk reduction for LV dysfunction
  - β Blockers – 37-84%
  - ACE Inhibition (ARB) – 71-96%
  - Statin – 23-87%
  - Dexrazoxane – 55-73%

Eut J Cancer
2013:49 2900-9
Cardio-Oncology Services UK-2016

- Lack of consensus on management
- 13% of UK centers with Cardio-Oncology clinics
- Wide variation in practice among centers
- Looked at Anthracycline, Trastuzumab, and Radiotherapy possible toxicity
- Cardio-Oncology clinics performed more intensive monitoring

**Need:**
- Organization of Cardio-Oncology Services
- Protocols/Guidelines for toxicity
- Measure patient outcomes

JACC 2016 Vol 67 Issue 12
Should we develop a curriculum for cardiovascular oncology?
Fellowship Training – what’s out there

- 7 Fellows in US / Canada - 2014
- No accreditation
- No internal funding
- No recognized structure to follow
Goals of the Curriculum

- Convey a knowledge base. Stimulate research.
- Integrate into mainstream cardiology and oncology training programs
- Reshape the mindset about traditional roles of cardiologists and oncologists.
- Graduates expand best practices outside the cloistered “cardio oncology centers”, improve practice, lessen disparities in practice.

Richard M. Steingart MD
Chief, Cardiology Service
Memorial Sloan-Kettering Cancer Center
Level 1 (Internal Medicine Residents)

- Basic knowledge of cancer agents and their potential to cause cardiac damage
- Imaging strategies – basic knowledge on cardiac imaging in oncology patients
- Basic understanding of treatment strategies for cancer patients experiencing cardiac toxicities
Level 2 (Medical/Cardiology Resident)

- For residents who wish to broaden their exposure to cardiac oncology patients
- More detailed assessment of patients
- Intermediate knowledge base
- More exposure to advanced cardiac imaging eg. advanced echocardiography (strain/3D)
- Understanding of the role of biomarkers in early detection of cardiac toxicity
Level 3 (Cardiac Oncology Fellow)

- 12-24 months of dedicated fellowship training
- Advanced knowledge of cancer agents and potential toxicities
- Broad exposure to in- and out-patients
- Training in biomarkers, advanced imaging
- Actively involved in research
Why do we need cardiac oncologists?

Left Ventricular Dysfunction in Patients Receiving Cardiotoxic Cancer Therapies: Are Clinicians Responding Optimally?

Yoon, Telli, Kao, Matsuda, Carlson, Witteles

What is Needed!

- **Network / Collaboration**
  - Facilitate networking: ICOS
  - Create working groups
  - Publicize Cardio-Oncology: websites, social media
  - Facilitate Research Collaborations: invite participation – group efforts

- **Clinical**
  - Centralize existing resources, create guidelines
  - Create a learning pathway

- **Training**
  - Develop a Fellowship program
  - Standardized Curriculum
Cancer and Cardiology – Survivors

- Where is the problem?
  - More cancer survivors
  - More heart damage
- More attention
  - Major cancer institutes
Need to foster cooperation between Cardiology and Oncology
Going Forward

- Absolute Necessity
  - Oncology leader
  - Cardiology leader

- Goal
  - Better Oncology care
  - Better Cardiology care

- End Result
  - Improved Quality of Life for cancer patient
International Registry

OCTOBER 2015
ICOS SUMMIT / NASHVILLE
A Work In Progress

Vanderbilt
University of Pennsylvania
University Hospital
(La Paz, Madrid)
Vancouver General Hospital

Collecting 400 Data Elements

Clinical Database
International Registry
October 2015 (Susan Dent)
ICOS Summit / Nashville

- DEMOGRAPHICS
- PAST MED HX
- FAM HX
- SOCIAL HX
- ONCOLOGY DATA
- CARDIOLOGY DATA

- Clinical
- Pathology
- Lab
- Interventions
- Treatment
- Protocol

Retrospective Data _________ Prospective Data
International Registry
October 2015 (Susan Dent)
ICOS Summit / Nashville

INTERNATIONAL REGISTRY

OUTCOME

Develop Mathematical Models to **Predict** Cardio Toxicity

Develop **Surveillance** Strategies for Cancer Survivors
Take Home Messages

- Development of Cardio Oncology (Cardiovascular Oncology)
- Close Cooperation with
  - Medical Oncology Services
- Develop Q/A Committee
- Collaboration with
  - Major Centers – (Outreach Programs)
  - Sloan Kettering
  - Vanderbilt
  - Ottawa Medical Center
Take Home Messages (Cont’d)

- Combined Conference
  - With Major Center
  - Ex. Video Conference

- Community Involvement
  - Private Practice (Family Physician, Cardiology)

- Program Participation with
  - Rheumatology
  - Neurology
  - Nephrology
  - ?
Take Home Messages (Cont’d)

• Image Evolution
  o ECHO Lab
  o MRI
  o PET
  o Nuclear Medicine

• Research Protocols (Pharmaceutical Support)

• Integration / Education
  o Medical Education
Take Home Messages (Cont’d)

- Development of Cardiovascular - Oncology Fellowship Program
- Expertise Requiring
  - Device Therapy / EP
  - Arrhythmia Management
  - PAD Management
  - Advanced CHF Program
Together we can make a difference in management of cancer patient and reduce the risk of developing heart failure.
CARDIOLOGY/ONCOLOGY PATIENT ACTIVITY
October 2015 through September 2016

- New Pts
- Total OV
In Conclusion

- We don’t know what we don’t know
- HOW can we make a difference?
  - NOT can we make a difference
- Final Question:
  - How important is a given medication for a patient?
  - Don’t abandon the patient - Figure it out!
- Are you going to close your eyes OR are you going to look?
Innovation

- We are in the innovation zone as described by Toby Cosgrove, MD in *The Cleveland Clinic Way*
- There needs to be collaboration across disciplines (multiple)
- We need new perspectives on old problems

I hope this has been a “pep talk” to encourage some of you to get involved in this fast changing field of **Cardiovascular Oncology**
The Future

- Restating words of Valentine Fuster, MD
  JACC, March 17, 2015 Editor
  - “Let us not.... fall into inertia... by acting as if our motor engine for curiosity and motivation is turned off.”
- “What we know is a drop, what we don’t know is an ocean” – Isaac Newton
- This is a fascinating field of which we know little.
Cancer survivor of today should not become the heart failure patient of tomorrow

-Mayo Clinic
The 17th Annual Benjamin Schuster, MD Colloquium
PRESENTED BY THE KETERING CARDIOVASCULAR INSTITUTE

Cardiovascular Oncology—Avoiding a Broken Heart

Wednesday, February 22, 2017
The Benjamin and Marian Schuster Performing Arts Center
Dayton, OH

SPEAKERS

Daniel Lenihan, MD, FACC
President, International CardiOncology Society - North America
Professor of Medicine
Director, Clinical Research Program, Vanderbilt Heart and Vascular Institute
Nashville, TN

Susan Dent, MD, FRCPC
President, Canadian Cardiac Oncology Network
Medical Oncologist, the Ottawa Hospital Cancer Center
Ottawa ON, Canada

John Groarke, MD, MSc, MPH
Cardiovascular medicine specialist at Brigham and Women's Hospital
Cardio-oncologist at Dana Farber Cancer Institute
Instructor of Medicine at Harvard Medical School
Boston, MA

$25 Registration fee (includes lunch)
3.5 CME ($50 fee for physicians)

To register and for more details visit:
ketteringhealth.org/2017Colloquium

Register Today @ ketteringhealth.org/2017colloquium
Questions?