Cardiovascular Effects of Cancer Treatment: What You Need to Know in Cardio-Oncology

Eric Yang, MD, FACC, FASE
Assistant Clinical Professor of Medicine
Director, UCLA Cardio-Oncology Program
Division of Cardiology
Department of Medicine
University of California at Los Angeles
Conflicts of Interest

• No conflicts of interest to disclose
Presentation Outline

• Current State of Cardiovascular Disease and Cancer
• Cardiotoxicity: Definitions
• Cardiotoxic Chemotherapeutic Agents: Cardiomyopathy
• Effects of Mediastinal Radiation Therapy
• Cardiotoxicity Surveillance During and After Cancer
• The Cardiooncology Clinic Concept
Current State of Cardiovascular Disease

• Estimated 92.1 million American adults (>1 in 3) have >/=1 type of CVD
  • 46.7 million are estimated to be >/= 60 years of age
  • CHD—16.5 million
  • MI (heart attack)—7.9 million
  • Heart failure—5.7 million
  • Stroke (all types)—7.2 million

• Prevalence of heart disease in 2014:
  • Whites 11.1%
  • Blacks or African Americans 10.3%
  • Hispanics or Latinos 7.8%
  • Asians 6.0%
  • American Indians or Alaska Natives 13.7%

• By 2030 43.9% of US population is projected to have some form of CVD
Current State of Cardiovascular Disease

• CVD listed as cause of death for 30.8% of all deaths in the United States in 2011 (1 of every 3 deaths)
  • Death rate of 229.6 per 100,000
• >2200 Americans die of CVD everyday
  • 1 death every 40 seconds
• CVD claims more lives each year than cancer and lung disease combined
• Leading cause of death in women ≥ 65 years of age
• 36% of deaths attributed to CVD before the age of 75 years (average life expectancy of 78.8 years)
Current State of Cancer

1,688,780 new cancer cases projected to occur in the US in 2017
  • 4,600 new cancer diagnoses each day

600,920 people projected to die from cancer in 2017
  • 1,650 cancer deaths per day

Most common causes of cancer death
  • Men: Lung and bronchus, prostate, and colorectal
  • Women: Lung and bronchus, breast, and colorectal
  • From 1991-2014 overall cancer death rates declined 25%
  • Overall 5 year survival improved from 63% in the 1960s to 90% in 2012 for breast cancer

Lifetime probability of being diagnosed with an invasive cancer
  • Men 43%
  • Women 38%
  • Risk higher for women in adults aged younger than 50 years because of breast, genital and thyroid malignancies
Trends in Death Rates Overall by Site and Gender in US
Cardiovascular and Cancer Deaths by Age in US, 2014
Age Adjusted Death Rates for White, Black, Hispanic Females in US, 2014
Current State of Cancer Survivors

Figure 1. Estimated Numbers of US Cancer Survivors by Site

As of January 1, 2014

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>2,975,970 (43%)</td>
<td>3,131,440 (41%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>621,430 (9%)</td>
<td>624,890 (8%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>516,570 (8%)</td>
<td>624,340 (8%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Melanoma</td>
</tr>
<tr>
<td>455,520 (7%)</td>
<td>528,860 (7%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Thyroid</td>
</tr>
<tr>
<td>297,820 (4%)</td>
<td>470,020 (6%)</td>
</tr>
<tr>
<td>Testis</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>244,110 (4%)</td>
<td>272,000 (4%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Uterine cervix</td>
</tr>
<tr>
<td>229,790 (3%)</td>
<td>244,180 (3%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>196,580 (3%)</td>
<td>233,510 (3%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>Oral cavity &amp; pharynx</td>
</tr>
<tr>
<td>194,140 (3%)</td>
<td>241,920 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Ovary</td>
</tr>
<tr>
<td>177,940 (3%)</td>
<td>199,900 (3%)</td>
</tr>
<tr>
<td><strong>All sites</strong></td>
<td><strong>All sites</strong></td>
</tr>
<tr>
<td>6,876,600</td>
<td>7,607,230</td>
</tr>
</tbody>
</table>

As of January 1, 2024

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>4,194,190 (45%)</td>
<td>3,951,930 (41%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>789,950 (8%)</td>
<td>771,070 (8%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melanoma</td>
</tr>
<tr>
<td>698,040 (7%)</td>
<td>756,980 (8%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>577,780 (6%)</td>
<td>756,980 (8%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>390,170 (4%)</td>
<td>360,220 (4%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>318,990 (3%)</td>
<td>289,400 (3%)</td>
</tr>
<tr>
<td>Testis</td>
<td>Cervix</td>
</tr>
<tr>
<td>308,000 (3%)</td>
<td>244,840 (3%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>Ovary</td>
</tr>
<tr>
<td>241,920 (3%)</td>
<td>236,320 (2%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>Kidney</td>
</tr>
<tr>
<td>240,530 (3%)</td>
<td>221,260 (2%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td><strong>All sites</strong></td>
</tr>
<tr>
<td>230,590 (2%)</td>
<td>9,602,590</td>
</tr>
</tbody>
</table>

Source: Data Modeling Branch, Division of Cancer Control and Population Sciences, National Cancer Institute.
American Cancer Society, Surveillance and Health Services Research, 2014
FACT SHEET: Investing in the National Cancer Moonshot

During his 2016 State of the Union Address, President Obama called on Vice President Biden to lead a new, national “Moonshot” initiative to eliminate cancer as we know it. Today, the White House is announcing a new $1 billion initiative to jumpstart this work.

Harnessing the Immune System to Fight Cancer

New drugs and methods of altering a patient’s own immune cells are helping some cancer patients—but not all—even when standard treatments fail.
Cancer Survivors

• Given advances in treatment and improved chemoradiation techniques survival continues to improve
  • Number of cancer survivors will approach 18 million by 2022
  • 67% of adults diagnosed with cancer will be alive in 5 years
  • 75% of children diagnosed with cancer will be alive in 10 years
• Many have had radiation and/or cancer treatments with potential for long-term cardiovascular toxicity
• Risk of cardiac death in patients treated with chemotherapy and radiotherapy is higher than actual risk of tumor recurrence
• Compared to general population, patients with a history of chemoradiation are more prone to CV events
  • 7 fold higher mortality rate
  • 15 fold increase rate of heart failure
  • 10 fold higher rates of CV disease
  • 9 fold higher rates of stroke
Cardiotoxicity: Definitions
What is Defined As Cardiotoxicity?

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCGE, version 3.0, LV systolic dysfunction&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Low</td>
</tr>
<tr>
<td>Grade 1 (mild); asymptomatic; resting EF 60%–50%; SF &lt;30%–24%</td>
<td>Grade 2 (moderate); asymptomatic; resting EF 50%–40%; SF &lt;30%–24%</td>
</tr>
<tr>
<td>CTCGE, version 4.03, LV systolic dysfunction&lt;sup&gt;18&lt;/sup&gt;</td>
<td>...</td>
</tr>
</tbody>
</table>

Any of 4 criteria confirm cardiac dysfunction: cardiomyopathy, reduced LVEF (global or more severe in the septum); symptoms of HF; signs associated with HF (S3 gallop and/or tachycardia); and decrease in LVEF from baseline ≥5% to <55% with accompanying signs or symptoms of HF or decline in LVEF ≥10% to <55% without accompanying signs or symptoms of HF

Cardiology derived

<table>
<thead>
<tr>
<th>ACC/AHA heart failure stage&lt;sup&gt;19&lt;/sup&gt;</th>
<th>Stage A, at risk (eg, patients receiving chemotherapy) but without structural heart disease or symptoms</th>
<th>Stage B, structural heart disease (hypertrophy, low EF, valve disease) but without signs or symptoms</th>
<th>Stage C, structural heart disease with prior or current symptoms</th>
<th>Stage D, refractory HF requiring specialized interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA symptom classification</td>
<td>Grade I, no limitation of activity</td>
<td>Grade II, mild limitation of activity; grade III, marked limitation of activity</td>
<td>Grade IV, confined to bed or chair</td>
<td></td>
</tr>
</tbody>
</table>

ACC/AHA indicates American College of Cardiology/American Heart Association; BNP, brain natriuretic peptide; CTCGE, Common Terminology Criteria for Adverse Events; EF, ejection fraction; HF, heart failure; IV, intravenous; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and SF, shortening fraction.
## Classification of Cardiotoxicity

<table>
<thead>
<tr>
<th></th>
<th><strong>Type I</strong> (damage)</th>
<th><strong>Type II</strong> (dysfunction)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prototype</strong></td>
<td>Doxorubicin</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td><strong>Noninvasive testing</strong></td>
<td>Global decrease in wall motion and ejection fraction</td>
<td>Global decrease in wall motion and ejection fraction</td>
</tr>
<tr>
<td><strong>Clinical course</strong></td>
<td>Stabilization possible but likely irreversible damage with poor tolerance to subsequent stressors</td>
<td>High likelihood of (near) complete recovery within months and good long-term prognosis</td>
</tr>
</tbody>
</table>
The “Multiple-Hit” Hypothesis

- Preexisting CV risk factor is itself a strong predictor for development of CV injury after chemotherapy, making overall CVD risk much higher
- During treatment phase of malignancies, CV risk factors ideally should be aggressively controlled
- General treatment guidelines in CV disorders may not be appropriate in cancer patients given limitations in traditional treatments.
Cardiotoxic Chemotherapeutic Agents: Cardiomyopathy
Cardiotoxic Chemotherapeutic Agents

• Anthracyclines
  • Doxorubicin (Adriamycin)
    • Used as the “standard” agent as isotoxic equivalent for risk stratification
    • Total cumulative dose mg/m²
  • Daunorubicin (Daunomycin)
    • Total dose X 1
  • Epirubicin (Ellence)
    • Total dose X 0.67
  • Idarubicin (Idamycin)
    • Total dose X 6
  • Mitoxantrone (Novantrone)
    • Total dose X 4

• Monoclonal Antibody-based Tyrosine Kinase inhibitors
  • Trastuzumab (Herceptin)
  • Bevacizumab (Avastin)
  • Pertuzumab (Perjeta)
  • Alemtuzumab (Lemtrada)

• Small-molecule Tyrosine Kinase Inhibitors
  • Dasatinib (Sprycel)
  • Imatinib (Gleevec)
  • Sunitinib (Sutent)
  • Sorafenib (Nexavar)
Anthracycline Cardiotoxicity

- Anthracycline agents used in more in 50% of childhood cancers as well as breast cancer
- Anthracycline based chemotherapy associated with much greater risk of developing cardiotoxicity (OR 5.43) than non-anthracycline regimens
- Multiple historical theories describing mechanisms, unclear until recent studies
  - Free-radical formation leading to DNA damage
  - Cardiac myocyte cell death
  - Cascade of neurohumoral mechanisms leading to myocardial injury and gradually heart failure
  - Inhibition of topoisomerase II
    - Induces breaks in DNA and ultimately cell death
Anthracycline Cardiotoxicity

- Clinical heart failure (HF)
  - Incidence of 30% at a median of 37 months post-treatment in adults
  - Acute cardiotoxicity occurs in less than 1% immediately after infusion; frequently reversible within weeks after discontinuation
  - Early-onset chronic cardiotoxicity occurs in 1.6-2.1% of patients during therapy or within first year after treatment
    - Peak incidence of 3 months post treatment
  - Late-onset chronic cardiotoxicity occurs at least 1 year after therapy in 1.6%-5% of patients
    - May occur as late as 10-20 years after first dose of treatment
- Rhythm disturbances can occur
Trastuzumab

- Human epidermal growth factor receptor-2 (HER2) encodes a transmembrane tyrosine kinase receptor that promotes cell proliferation and survival
- HER2 overexpression/amplification is seen in 20-30% of breast cancers and is associated with an aggressive cancer phenotype
- Trastuzumab is a HER2 directed monoclonal antibody
  - 40-50% reduction in recurrence of breast cancer
  - 30% reduction in risk of death from breast cancer
Trastuzumab Induced Cardiotoxicity

• **Trastuzumab (Herceptin)**
  - High incidence of cardiotoxicity ranging from 2-28%
    - Reduction in left ventricular systolic function or heart failure
  - Higher incidence in combination with anthracyclines (27% versus 8%)
  - Outcomes more favorable than anthracycline induced cardiotoxicity
  - Most cardiotoxic manifestations recover with discontinuation of treatment
  - Mechanism thought to be due to interfering with growth and repair of cardiac myocytes
Adjuvant Trastuzumab in HER2-Positive Breast Cancer

Table 4. Cardiac Risk Factors and Events.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>AC-T (N = 1073)</th>
<th>AC-T plus Trastuzumab (N = 1074)</th>
<th>TCH (N = 1075)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>38 (3.5)</td>
<td>36 (3.4)</td>
<td>28 (2.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>178 (16.6)</td>
<td>178 (16.6)</td>
<td>190 (17.7)</td>
</tr>
<tr>
<td>Obesity†</td>
<td>214 (19.9)</td>
<td>242 (22.5)</td>
<td>234 (21.8)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>54 (5.0)</td>
<td>47 (4.4)</td>
<td>43 (4.0)</td>
</tr>
<tr>
<td>Left-side radiotherapy</td>
<td>378 (35.2)</td>
<td>349 (32.5)</td>
<td>364 (33.9)</td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac-related death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart failure‡</td>
<td>7 (0.7)</td>
<td>21 (2.0)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>&gt;10% relative reduction in left ventricular ejection fraction‖</td>
<td>114 (11.2)</td>
<td>194 (18.6)</td>
<td>97 (9.4)</td>
</tr>
</tbody>
</table>

* AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and trastuzumab.

Figure 2. Left Ventricular Ejection Fraction (LVEF) at 48 Months.
Shown are the values for the mean left ventricular ejection fraction for 3086 of 3222 patients (96%) in the three study groups. At the time of this analysis, sufficient numbers of LVEF determinations were not yet available beyond 48 months. AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and trastuzumab.

Trastuzumab Induced Cardiotoxicity

• If 1000 women received standard chemotherapy without trastuzumab
  • About 900 would survive
  • About 5 would have experienced cardiotoxicity

• If 1000 women received standard chemotherapy with trastuzumab for 1 year
  • 33 more women would have their lives prolonged
  • 95 more women will not experience cancer relapse
  • 21 more women would have cardiotoxicity
VEGF Signaling Pathway Tyrosine Kinase Inhibitors (TKI)

- **Sunitinib and Sorafenib**
  - Renal cell carcinoma and gastrointestinal stromal tumor (sunitinib)
  - Renal cell carcinoma, hepatocellular carcinoma, thyroid carcinoma (sorafenib)

- **Known cardiotoxic effects of hypertension and LV dysfunction**
  - Hypertension incidence of 19-47%
  - Cardiac dysfunction 4-8%
  - Incidence of asymptomatic LVEF decline ≥ 10% of up to 28%

- **Act by inhibiting the vascular endothelial growth factor (VEGF) signaling pathway**

- **TKI competitively bind to and inhibit the ATP binding pocket which is conserved across >500 kinases expressed in humans**
Effects of Mediastinal Radiation Therapy
Introduction

• Radiation therapy used in management of more than 50% of cancer patients

• Significant survival benefit with adjuvant radiation therapy
  • Breast Cancer following breast conserving therapy: 50% reduction in disease recurrence and 17% reduction in death
  • Hodgkin’s lymphoma: 5 year survival rates >85% along with chemotherapy

• Radiation therapy used to induce double-stranded DNA breaks in malignant cells causing apoptosis or preventing cellular division

• Radiation dose measured in Gray units
  • 1 gray (Gy) is absorption of 1 J of ionizing radiation energy by 1 kg of tissue

• Overall decreased radiation doses due to advances in CT planning systems, intensity-modulated radiotherapy and helical tomotherapy
## Table 1  Relative risks of RIHD in cancer survivors

<table>
<thead>
<tr>
<th>Types</th>
<th>Hodgkin’s disease relative risk</th>
<th>Breast cancer relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIHD</td>
<td>&gt;6.3</td>
<td>2–5.9</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>4.2–6.7</td>
<td>1–2.3</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2.2–12.7</td>
<td>0.9–2</td>
</tr>
</tbody>
</table>

The reported relative risk of RIHD is proportional to radiation dose and time to exposure.
Mechanisms of Radiation Induced Cardiovascular Disease

Figure 1: Pathophysiological manifestations of radiation-induced heart disease for different radiosensitive structures within the heart. LV, Left ventricle; RT, radiotherapy.
Mediastinal Radiation Effects

- **Pericardium**
  - Pericarditis less frequent due to decreased radiation doses (total dose < 30 Gys)
  - Can lead to pericardial constriction, effusion, tamponade

- **Cardiomyopathy**
  - Myocardial infiltration
  - Mean dose 35.9 Gys
  - Mean 14.1 years

- **Valvular Disease**
  - Prevalence of valvular fibrosis 70-80% after radiation doses > 35 Gy
  - Mean time to diagnosis 16.5 years post-therapy

- **Arrhythmias**
  - AV nodal block
  - Sinus node dysfunction
  - Infranodal block
  - QT prolongation
  - Tachyarrhythmias
Mediastinal Radiation Effects

• **Coronary Artery Disease**
  - Elevated risk of radiation induced CAD with radiation dose \( \geq 30 \) Gy
  - Lesions tend to be proximal and ostial
  - Consists of premature fibrosis and accelerated atherosclerosis
  - Distribution of arteries affected tend to be anterior with anterior weighted therapy

• **Dysautonomia**
  - Tachycardia, loss of circadian rhythm
  - Perception of cardiac chest pain may be blunted
Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

- Population-based case-control study of major coronary events (MI, coronary revascularization, death from IHD)
- 2168 women who underwent radiotherapy for breast cancer from 1958-2001 in Sweden and Denmark
- 963 women had major coronary events and 1205 controls
- Mean radiation doses to whole heart and to the left anterior descending coronary artery estimated from radiotherapy chart
- Overall average mean doses to whole heart was 4.9 Gy (0.03-27.72)
- Rates of major coronary events increased linearly with mean dose to heart by 7.4% per gray
- Increase started within the first 5 years after radiotherapy and continued into the third decade

![Graph showing the relationship between mean dose of radiation to the heart and percent increase in rate of major coronary events.](image)

*Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.*
• Retrospective cohort study of 2524 Dutch HL survivors
• Data collected from hospital records and general practitioners
• Mean age of diagnosis 27.3 years
• Treated from 1965-1995 and survived 5 years
• Median anthracycline cumulative dose 210 mg/m2
Radiation Valvulopathy

- Mediastinal radiation exposure can lead to accelerated fibrosis of valves
- Left sided valves are commonly more affected
  - Aortic valve
  - Mitral Valve
- Both significant closure (stenosis) and regurgitation can occur leading to heart failure
- Accompanying CAD, fibrotic lung disease and other comorbidities make patients higher risk for surgery
Cardiotoxicity Surveillance During and After Cancer
• 201 consecutive patients with LVEF \leq 45\% due to anthracyclines
• Enalapril (goal dose 20 mg/day) and carvedilol (50 mg/day) initiated as tolerated
  - 36\% only received ACE-I
• 42\% responders, 13\% partial responders, 45\% were nonresponders
• Percentage of responders decreased as time from end of CMT to start of HF Tx increased
Anthracycline-Induced Cardiomyopathy
Clinical Relevance and Response to Pharmacologic Therapy

Daniela Cardinale, MD, PhD,* Alessandro Colombo, MD,* Giuseppina Lamantia, MD,* Nicola Colombo, MD,* Maurizio Civelli, MD,* Gaia De Giacomi, MD,* Mara Rubino, MD,† Fabrizio Veglia, PhD,† Cesare Fiorentini, MD,† Carlo M. Cipolla, MD*

Milan, Italy

Figure 1
Percentage of Responders According to the Time Elapsed From AC Administration and Start of HF Therapy

AC = anthracyclines; HF = heart failure.

Figure 2
Cumulative Cardiac Event Rate During the Study Follow-Up

2-year Kaplan-Meier analysis for major adverse cardiac events in the 3 study groups. p = 0.0003 (log-rank test).
Prospective study of 2625 patients receiving anthracycline therapy

Mean age 50+-13 years, 74% women

51% breast cancer, 28% NHL

LVEF assessed at baseline, every 3 mos during chemotherapy and every 6 months over 4 years

For LVEF decrease >10 and <50%, HF therapy initiated

End chemotherapy and cumulative anthracycline dose independent correlates of cardiotoxicity

Active/Future Avenues of Research

Figure 1. Proposed mechanisms and potential cardioprotective therapies for cardiotoxicity due to anthracyclines and ErbB inhibitors. A, Mechanisms of anthracycline-induced cardiotoxicity. B, Potential cardioprotective therapies target the described mechanisms of cardiotoxicity. C, Mechanisms of ErbB inhibitor-induced cardiotoxicity by trastuzumab. ACE indicates angiotensin-converting enzyme; ERK1/2, extracellular signal-regulated kinase 1/2; MAPK, mitogen-activated protein kinase; NRG-1, neuregulin-1; PI3K, phosphoinositide 3-kinase; Top2β, topoisomerase IIβ.

Consensus Explosion

Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers American Society of Clinical Oncology Clinical Practice Guideline
Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

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

Recommendation 1.1. It is recommended that patients with cancer who meet any of the following criteria should be considered at increased risk for developing cardiac dysfunction.

- Treatment that includes any of the following:
  - High-dose anthracycline (eg, doxorubicin ≥ 250 mg/m², epirubicin ≥ 600 mg/m²)
  - High-dose radiotherapy (RT; ≥ 30 Gy) where the heart is in the treatment field
  - Lower-dose anthracycline (eg, doxorubicin < 250 mg/m², epirubicin < 600 mg/m²) in combination with lower-dose RT (< 30 Gy) where the heart is in the treatment field
Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

- Treatment with lower-dose anthracycline (eg, doxorubicin < 250 mg/m², epirubicin < 600 mg/m²) or trastuzumab alone, and presence of any of the following risk factors:
  - Multiple cardiovascular risk factors (≥ two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
  - Older age (≥ 60 years) at cancer treatment
  - Compromised cardiac function (eg, borderline low left ventricular ejection fraction [50% to 55%], history of myocardial infarction, ≥ moderate valvular heart disease) at any time before or during treatment
- Treatment with lower-dose anthracycline (eg, doxorubicin < 250 mg/m², epirubicin < 600 mg/m²) followed by trastuzumab (sequential therapy)
(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
Health Screening

- Lifelong screening for cardiovascular disease is critical in patients with a history of chemotherapy and/or radiation therapy
  - Heterogenous consensus and guideline statements
  - Children Oncology Group Long Term Followup Guidelines (2013)
  - ASE/ESC Consensus for Multimodality Imaging for Patients After Radiotherapy (2013)
  - ASE/ESC Consensus for Multimodality Imaging of Adults During and After Cancer Treatment (2014) (gives recommendations within 6 months post treatment)
  - ASCO Prevention and Monitoring of Cardiac Dysfunction of Survivors of Cancer Clinical Practice Guidelines (2017) states inadequate evidence to provide recommendations for long term surveillance
- Cancer Survivorship visits are invaluable in providing education in secondary malignancy screening, referral for evaluation of relevant medical issues, and for cardiovascular evaluation if indicated
- Primary prevention is better than secondary prevention
- UCLA-LIVESTRONG Survivorship Center of Excellence
Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging
Figure 13  Initiation of a regimen potentially associated with type I toxicity. A baseline evaluation including measurements of LVEF, GLS, and troponins is recommended. If any are abnormal, a cardiology consultation is recommended. Follow-up is recommended at the completion of therapy and 6 months later for doses < 240 mg/m² or its equivalent. Once this dose is exceeded, measurements of LVEF, GLS, and troponin are recommended before each additional 50 mg/m².
Initiation of trastuzumab

Baseline evaluation of LVEF
3DE (preferred) / 2DE (consider contrast)
GLS or Troponin I

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

Cardiology consultation
F/U every 3 months during therapy

LVEF > 53%
GLS > LLN**
- Troponins

Cardiology consultation
F/U every 3 months during therapy

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

Figure 14 Initiation of trastuzumab. A baseline evaluation including measurements of LVEF, GLS, and troponin is recommended. If any are abnormal, a cardiology consultation is recommended. Measurements of LVEF, GLS, and troponin are recommended every 3 months.

Initiation of trastuzumab after regimen associated with Type I toxicity

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

LVEF < 53%*
GLS < LLN**
- Troponins

Cardiology consultation
F/U every 3 months during therapy, and 6 months later

LVEF > 53%
GLS > LLN**
- Troponins

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

Figure 15 Initiation of trastuzumab after regimen associated with type I toxicity. A baseline evaluation including measurements of LVEF, GLS, and troponin is recommended. If any are abnormal, a cardiology consultation is recommended. Measurements of LVEF, GLS, and troponin are recommended every 3 months during therapy and 6 months later.
Health Screening

• Lifelong screening for cardiovascular disease is critical in patients with a history of chemotherapy and/or radiation therapy
  • Heterogenous consensus and guideline statements
  • Children Oncology Group Long Term Followup Guidelines (2013)
  • NCCN Survivorship Clinical Practice Guidelines (2015)
  • ASE/ESC Consensus for Multimodality Imaging for Patients After Radiotherapy (2013)
  • ASE/ESC Consensus for Multimodality Imaging of Adults During and After Cancer Treatment (2014)

• Cancer Survivorship visits are invaluable in providing education in secondary malignancy screening, referral for evaluation of relevant medical issues, and for cardiovascular evaluation if indicated

• Primary prevention is better than secondary prevention

• UCLA-LIVESTRONG Survivorship Center of Excellence
Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group


Cardiomyopathy surveillance is recommended for high risk survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis and continued every 5 years thereafter.

More frequent cardiomyopathy surveillance is reasonable for high risk survivors.

Lifelong cardiomyopathy surveillance may be reasonable for high risk survivors.

Echocardiography

- Assessment of left ventricular systolic and diastolic function
- Valvular disease
- Pericardial disease
- Not sensitive for detection of subclinical cardiac disease
- 2014 systematic review

  - Tissue doppler-based strain imaging—peak systolic longitudinal strain rate most consistently detects early myocardial changes
  - Speckle tracking—peak systolic global longitudinal strain rate (10-15% early reduction) most predictive of cardiotoxicity and possible worse prognosis
Cardiotoxicity Surveillance: A Multidisciplinary Effort
Tip of the Iceberg…

- Radiation (cardiac ischemia, valvular disease, pericardial disease, arrhythmia)
- Anthracyclines (cardiomyopathy)
- Anti-metabolites (SFU) (ischemia, vasospasm)
- Her2-targeted therapies (cardiomyopathy)
- VSP inhibitors (hypertension, heart failure, thrombosis)
Summary

• Advances in cancer therapy have led to significant increases in long term survival, leading to a large population of cancer survivors that represent a “special population” that warrants more aggressive cardiovascular screening and surveillance.

• Collaboration and communication between cardiology and hematology/oncologists is essential to provide optimal cardiovascular care and surveillance for patients before, during, and after (and way after) cancer treatments with potentially cardiotoxic therapies.
Thank You

Questions?

Eric Yang, MD, FACC, FASE
ehyang@mednet.ucla.edu
UCLA Cardiovascular Center
100 UCLA Medical Plaza, Suite 630
Los Angeles, CA 90095
310.809.1184 (cell)
24735 (pager)
Cardio-Oncology Clinic
Concept
ACC Top Cardiology Stories of 2014

Top developments in Cardiology anticipated for 2014

• Affordable Care Act Individual Mandate for health insurance coverage
• Sustainable Growth Rate Permanent Fix
• Development of PCSK9 inhibitors
• Implementation of ACC/AHA prevention guidelines
• Rollout of mitral valve clip
• Expanded use of novel oral anticoagulants in AF or VTE disease
• Results of Dual Antiplatelet Therapy Study (DAPT)
• Potential new therapy for refractory hypertension
• Continued growth of cardiooncology

Cardiooncology/Oncocardiology Programs

Heart disease remains the greatest single great threat in diagnosis and treatment for cancer patients. The Cardio-Oncology Program is designed to support patients with heart disease. This unique clinic brings together expert cardiology care and oncology care. Our clinic specializes in heart disease by a comprehensive evaluation.

Clinical Population
All patients being considered for potentially cardiotoxic chemotherapy or chest radiation, especially those who have prior cardiac history, should undergo detailed cardiovascular evaluation prior to treatment.

Candidates for referral include:
- All cancer patients before initiating potentially cardiotoxic treatment, specifically anthracyclines, trastuzumab, VEGF inhibitors and radiation therapy
- Patients with pre-existing cardiovascular issues who have newly diagnosed cancer and need to be shepherded safely through the medical and surgical treatment of their cancer.
- Patients who may have cardiac side effects from traditional cancer therapies, such as anthracyclines and radiation. Working closely with the oncologist, we will monitor and help adjust therapy for these patients with the goal of minimizing cardiovascular complications while effectively treating the underlying cancer.
- Patients being treated with novel molecular targeted therapies who may have potential adverse cardiovascular effects. The onco-cardiology team will conduct research with the objective of improving the understanding of cardiotoxicity mechanisms of novel cancer drugs. This work may help identify patients at risk for developing cardiovascular complications and may also help design enhanced and less cardiotoxic cancer treatments.
- Patients who are long-term cancer survivors and need to be screened and treated for cardiovascular conditions that may or may not be related to their past cancer treatment.
Growth of Cardio-oncology Research

FIGURE 2: PubMed Citations in "Cardio-Oncology"

Search term "cardio oncology"

Number of PubMed citations using search term "cardio oncology" by year.
Goals of Cardiooncology Program

- Evaluate and assess risk for patients with newly diagnosed malignancy or those undergoing active treatment with potential cardiotoxic effects and determine short and long term surveillance strategies with most up to date data possible
- Assist in minimizing cardiotoxic manifestations and optimizing therapy on patients with established heart disease during treatment
- Assess long term risk and manifestations of chemoradiation therapy in cancer survivors and promote primary/secondary prevention
- Refer to subspecialty care within Cardiology if indicated
- Provide same day imaging (ie echo) and electrophysiology referral for dysautonomias, arrhythmias
- Provide input at tumor boards and multidisciplinary meetings
- **Provide ongoing multidisciplinary care and promote research collaborations between Hematology/Oncology and Cardiology in identifying individuals at risk for cardiotoxicity, implementing effective cardioprotective interventions to attenuate risk for cardiotoxicity during treatment, and developing surveillance strategies to detect short- and long-term subclinical/clinical cardiac disease.**
Planned Structure

• 2 Half days a week, also integrated into my general clinical practice (already happening)

• Depending on volume can expand further

• Offering potentially same day imaging surveillance, suspected cardiotoxicity/dysfunction (echo, stress testing)

• EP consultation for dysautonomias (ie Dr. Olujimi Ajijola)

• Referral to different subspecialists for further subspecialty care depending on specific needs (ie Women’s Health, Interventional, Imaging, Structural, Electrophysiology, etc)

• Inquire about having “ambassadors” from each section of Hematology/Oncology (ie lymphoma, leukemia, breast CA, sarcoma, etc) for ongoing feedback and discussions on how to improve the clinic experiencee work flow, etc.
THREE CATEGORIES OF PATIENTS

• Pre Treatment Population
• Peri Treatment Population
• Post Treatment Population (Cancer Survivor)
Pre Treatment Population

• Newly diagnosed malignancy with treatment plan being exposed to potential cardiotoxic therapies with prior established cardiac risk factors
  • Anthracyclines
  • Monoclonal Ab (ie trastuzumab)
  • TKIs
  • Fluoropyrimidines
  • New agents with possible cardiac safety concerns
  • Any of above + mediastinal radiation therapy

• Prior cardiac risk factors (1 or more of the above):
  • CAD
  • Valvular disease of at least moderate severity
  • Known prior arrhythmias (ie SVT, atrial fibrillation, flutter)
  • Prolonged QTc at baseline
  • Prior exposure to cardiotoxic agents
  • Structural heart disease
  • Congestive heart failure (LVEF <50%) or concerns for heart failure with preserved ejection fraction (HFpEF)

• Any concern of primary Heme/Onc attending in general free to refer
Peri Treatment Population

• Development of any cardiac symptoms (whether therapy induced or due to native disease) during treatment
  • Signs of ischemia/angina (TKIs, fluoropyrimidines)
  • Congestive heart failure
  • Surveillance imaging showing decrease of LVEF <53%
  • Surveillance imaging showing discordant/inconsistent findings of cardiac function
  • Prolonged QTc during therapy
  • Arrhythmias during treatment (ie AF, SVT, VT)
  • Peripheral arterial events during treatments (ie thrombosis)
  • Hypertension during TKI/VGEF treatments
  • Pericardial effusion with concern for hemodynamic compromise
  • Provide cardiac safety surveillance in patients undergoing clinical trials with new chemotherapeutic agents

• Any concern of primary Heme/Onc attending in general free to refer
Post Treatment Population

- Post treatment if prognosis favorable can refer for following indications:
  - Counseling on data regarding long term cardiomyopathy surveillance (ie anthracyclines, radiation) as well as for valvular disease
  - Abnormal findings found on stress testing/echocardiography post treatment
  - Symptoms concerning to be of cardiac etiology (ie chest pain, dyspnea, etc).
  - Concern for chemoradiation induced dysautonomias (Dr. Olujimi Ajijola of EP)
  - Primary prevention referrals for aggressive treatment and detection of accelerated atherosclerotic/cardiovascular disease (ie radiation therapy patients)
  - Women of childbearing age with prior history of chemotherapy/radiation history seeking to become pregnant to follow for cardiac monitoring/counseling
- Any concern of primary Heme/Onc attending in general free to refer
Cardio-Oncology Team Model Example

The various responsibilities of a cardio-oncologist are diagrammed, showing the constant feedback and interactive process to effect integrated patient care. Modified with permission from Okwuosa TM, Akhter N, Williams KA, DeCara JM. Building a cardio-oncology program in a small to medium-sized, nonprimary cancer center, academic hospital in the USA: challenges and pitfalls. Future Cardiol 2015;11:1-8.
CARDIO-ONCOLOGY CLINIC STATISTICS
JUNE 2016-MAY 2017
Cardio-Oncology Clinic Volume at Westwood-UCLA

Clinic “Go Live”

**Includes repeat visits of same patient**
Cardiooncology Clinic Demographic by Gender

- Male: 58%
- Female: 42%

Cardiooncology Clinic Demographic by Timing of Visit to Cancer Treatment

- Pre-Treatment: 63%
- Post-Treatment: 35%
Cardiooncology Clinic Volume By Cancer Type

- Breast: 22%
- Lung: 2%
- Lymphoma/Leukemia: 12%
- Gastrointestinal/hepatobiliary: 0%
- Brain: 4%
- Genitourinary: 1%
- Sarcoma: 5%
- Hematologic (MM, MGUS): 0%
- Gynecologic: 5%
- ENT: 0%
- Thyroid: 7%
- Adrenal: 36%
Cardio-Oncology Clinic Volume by Chief Complaint

- Preop
- CAD or ischemic sx
- CHF
- Arrhythmias
- Dysautonomia
- Surveillance
- Hypertension
- Pericardial/Myocarditis
- Valvular Disease
Cardiooncology Clinics and Project Expansion Efforts

- Ronald Reagan-UCLA (Westwood)
  - Eric Yang, M.D.
  - Gabriel Vorobiof, M.D.
  - Olujimi Ajijola, M.D., Ph.D.
  (Dysautonomia/Dysrhythmia evaluations)

- Santa Monica-UCLA
  - Melkon Hacobian, M.D.

- UCLA-Ventura, Simi Valley
  - Megha Agarwal, M.D.

- UCLA-Santa Clarita
  - Nidhi Thareja, M.D.

- UCLA-Encino
  - Boris Arbit, M.D.

- Cardiovascular Fellows in Cardiooncology Clinic
  - Duc Do, M.D.
  - Vinisha Garg, M.D.
  - Brian West, M.D.
Selected Cardio-Oncology Publications by UCLA Faculty/Housestaff

- **2017**

- **2016**

Authors’ Names in Bold Denote UCLA Authors
Selected Cardio-Oncology Publications by UCLA Faculty/Housestaff

• 2015

• 2014

• 2013

Authors’ Names in Bold Denote UCLA Authors
Ongoing Research Projects/Collaborations

- **Section Editor for Cardio-oncology Section, Current Oncology Reports**
  - Invite local and national authorities to provide review articles on topics of interest within the cardiooncology field
  - Platform for residents, fellows, and faculty to contribute review articles

- **MADIT-CHIC (Multicenter Automatic Defibrillator Implantation Trial - Chemotherapy-Induced Cardiomyopathy)**
  - Observational trial evaluating echocardiographic and symptom endpoints of patients who undergo cardiac resynchronization therapy from chemotherapy induced cardiotoxicity
  - Co-PI: Noel Boyle, M.D., Ph.D., Research Coordinator: Julie Sorg, NP
  - [https://clinicaltrials.gov/ct2/show/NCT02164721](https://clinicaltrials.gov/ct2/show/NCT02164721)

- **Phase I-II study looking at feasibility of perioperative beta blockade (propranolol) in patients with newly diagnosed breast cancer undergoing surgery**
  - Explore effects of BB in expression of pro-inflammatory and pro-metastatic genes in tumor microenvironment
  - Collaborators: Julienne Bower, PhD, Patricia Ganz, MD, Olujimi Ajijola, MD, PhD

- **Cardiac MRI studies in active cardiotoxicity and cancer survivors**
  - Collaborators: Kim-Lien Nguyen, M.D. (West LA-VA), Paul Finn, M.D.

- **Dysautonomia assessment of chemoradiation survivors**
  - Noninvasive ANSAR testing in cancer survivors with suspected dysautonomias
  - Collaborator: Olujimi Ajijola, MD, PhD

- **Ongoing research collaborations with other Cardiooncology centers (ie Mayo, MD Anderson, Missouri, City of Hope, etc)**
Thank You

Questions?

Eric Yang, MD, FACC, FASE
ehyang@mednet.ucla.edu
UCLA Cardiovascular Center
100 UCLA Medical Plaza, Suite 630
Los Angeles, CA 90095
310.809.1184 (cell)
24735 (pager)