CARDIO-ONCOLOGY

THE BASICS

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Cardio-Oncology: Lets start with a horror story
65 YEAR OLD female with undiagnosed breast cancer and undiagnosed ischemic heart disease

Scenario 1

• The patient reaches an oncologist first, has a mammogram that shows a tumor and further investigations show a HER2-positive breast CA

• She is started on chemo with doxorubicin followed by trastuzumab

• She develops trastuzumab/anthracycline induced cardiotoxicity a few months later

• Progressive and irreversible heart failure ensues
65 YEAR OLD female with undiagnosed breast cancer and undiagnosed ischemic heart disease

SCENARIO 2

• Patient reaches **cardiologist** first who diagnoses ischemic heart disease with mild LV dysfunction
• Patient has a positive stress test, undergoes PCI of mid LAD lesion, and started on dual antiplatelet therapy
• Few months later she is diagnosed with breast cancer on a mammogram
• Conservative non cardiotoxic chemo without trastuzumab or anthracyclines is initiated and her cancer progresses
65 YEAR OLD female with undiagnosed breast cancer and undiagnosed ischemic heart disease

**SCENARIO 3**

- Patient is seen by a **multi disciplinary cardio oncology** team.
- Investigations by oncologist reveals HER 2+ breast CA.
- Cardiac pre screening by cardiologist reveals CAD, mild LV dysfunction.
- After discussion of risks among the team and with the patient, medical therapy started & optimized for CAD, mild CHF. Chemotherapy is administered with liposomal anthracyclines to lower cardiotoxicity risk, followed by trastuzumab with close cardiac monitoring clinically and echocardiographically.
- Patient is successfully managed for both conditions and has an optimistic chance of survival with a good quality of life.
Cardio-Oncology: The Math
In June 2016, 15.5 million people diagnosed with cancer are still living in the United States.

69% of these cancer survivors will have a 5-year life expectancy due to advances in early detection and treatment of cancer.

Out of the survivors > 50 years of age, >50% of men and 40% of women will develop cardiovascular disease during their remaining lifespan.
> 80% of children and adolescents who are treated for cancer become long-term survivors.

In 2013, there were approximately 420,000 survivors of pediatric cancer in the US, by 2020 it will be 500,000.

As per the Childhood Cancer Survivor Study (CCSS) cohort, the cardiac mortality in these childhood cancer survivors was 7-fold higher and a 15-fold lifetime risk of developing HF compared to age-matched population.
3: Because we have been bad at managing cardio-toxicity in our cancer patients

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

Geoffrey J. Yoon, MD,* Melinda L. Telli, MD,† David P. Kao, MD,‡ Kelly Y. Matsuda, PharmD,* Robert W. Carlson, MD,† Ronald M. Witteles, MD*
Stanford, California; and Denver, Colorado

Objectives
The purpose of this study was to examine treatment practices for cancer therapy-associated decreased left ventricular ejection fraction (LVEF) detected on echocardiography and whether management was consistent with American College of Cardiology/American Heart Association guidelines.

Background
Patients treated with anthracyclines or trastuzumab are at risk of cardiotoxicity. Decreased LVEF represents a Class I indication for drug intervention according to American College of Cardiology/American Heart Association guidelines.

Methods
Patients receiving anthracycline or trastuzumab at Stanford University from October 2005 to October 2007 and who had undergone echocardiography before and after receiving an anthracycline or trastuzumab were identified. Chart review examined chemotherapy regimens, cardiac risk factors, imaging results, concomitant medications, and cardiology consultations.

Results
Eighty-eight patients received therapy with an anthracycline or trastuzumab and had a pre-treatment and follow-up echocardiogram. Ninety-two percent were treated with anthracyclines, 17% with trastuzumab after an anthracycline, and 8% with trastuzumab without previous treatment with anthracycline. Mean baseline LVEF was 60%, with 14% having a baseline <55%. Forty percent had decreased LVEF (<55%) after anthracycline and/or trastuzumab treatment. Of these patients, 40% received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, 51% beta-blocker therapy, and 54% cardiology consultation. Of patients with asymptomatic decreased LVEF, 31% received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, 35% beta-blocker therapy, and 42% cardiology consultation. Of those with symptomatic decreased LVEF, 67% received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, 100% beta-blocker therapy, and 89% cardiology consultation.

Conclusions
Many cancer survivors are not receiving treatment consistent with heart failure guidelines. There is substantial opportunity for collaboration between oncologists and cardiologists to improve the care of oncology patients receiving cardiotoxic therapy. (J Am Coll Cardiol 2010;56:1644–50) © 2010 by the American College of Cardiology Foundation
LONG TERM SURVIVAL OF CARDIOMYOPATHY DEPENDING ON ETIOLOGY

Adjusted Kaplan–Meier Estimates of Survival According to the Underlying Cause of Cardiomyopathy
Cardio-Oncology: The History

"You got a "C" in History?? How hard could it be?"
Historical perspective: the Anthracycline story

- Anthracyclines have been used as antineoplastic agents for many cancers since they were first isolated from the pigment-producing *Streptomyces peucetius* early in the 1960s.
- The original trade name was Adriablastina owing to its discovery along the shores of the Adriatic sea.
- Adriamycin was then renamed Doxorubicin as the term mycin identified it as an antibiotic.
Early observations in 1979 by Von Hoff the cumulative dose that correlated with 5% of the patients developing HF was approx 550mg/m2 and for 2 decades that became the nominal upper limit dose for doxorubicin.
2003: Dose related Cardiotoxic effect of Doxo was worse than we thought

Fig. 1. The original Von Hoff curve (solid) showing low expression of cardiotoxicity at low cumulative doses with rapid rise as cumulative doses exceeded 500 mg/m². Subsequent analysis demonstrated that doxorubicin was more cardiotoxic than initially appreciated, as depicted by the dashed curve based on data from Swain and colleagues²¹ and from the MD Anderson Cancer Center. *(Data from Von Hoff D, Layard M, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979;91:710–7; Swain S, Whaley F, Ewer M. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97:2869–79.)*
Billingham Score: the microscopic correlation of cardiotoxicity

Billingham at Stanford devised a grading of toxicity based on myocardial biopsy findings under Electron Microscopy:

1. Even **lower doses** 300-500 mg/m² showed cardiotoxicity
2. **Patients with extremes of age, prior anthracycline exposure, radiation exposure etc showed more cardiotoxicity and helped us identify the risk factors** for anthracycline cardiotoxicity
3. Epirubicin and liposomal doxorubicin showed lower biopsy grades
4. Also helped define **Type I vs Type II cardiotoxicity**

![Microscopic images of myocardium](image-url)
## Type I and Type II Cardiotoxicity

<table>
<thead>
<tr>
<th></th>
<th>Type I (eg, Doxorubicin)</th>
<th>Type II (eg, Trastuzumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocyte death; permanent damage starts with first dose; bad prognosis(^1)</td>
<td>Myocyte dysfunction; predominantly reversible; good prognosis(^1)</td>
<td></td>
</tr>
<tr>
<td>Biopsy changes typical of anthracyclines(^1)</td>
<td>No typical anthracycline-like biopsy changes(^1)</td>
<td></td>
</tr>
<tr>
<td>Cumulative-dose related(^1)</td>
<td>Not dose related(^1)</td>
<td></td>
</tr>
<tr>
<td>Risk factors(^2)</td>
<td>Risk factors(^2-4)</td>
<td></td>
</tr>
<tr>
<td>Combination CT</td>
<td>Prior or concomitant anthracyclines</td>
<td></td>
</tr>
<tr>
<td>Prior or concomitant RT</td>
<td>Prior or concomitant paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Previous cardiac disease</td>
<td>Previous cardiac disease</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Obesity (BMI &gt; 25 kg/m(^2))</td>
<td></td>
</tr>
</tbody>
</table>


### Table 1: Proposed classification of chemotherapy-related cardiomyopathy

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Prototype</th>
<th>Findings on endomyocardial biopsy (electron microscopy)</th>
<th>Cumulative dose relationship</th>
<th>Reversibility</th>
<th>Associated with increased cardiovascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Doxorubicin (anthracycline)</td>
<td>Vacuoles, sarcomere disruption, necrosis</td>
<td>Yes</td>
<td>No (might respond to very early treatment)</td>
<td>Yes</td>
</tr>
<tr>
<td>Type II</td>
<td>Trastuzumab (monoclonal antibody)</td>
<td>Benign ultrastructural appearance</td>
<td>No</td>
<td>Yes, in most cases</td>
<td>No</td>
</tr>
</tbody>
</table>
That was the “Historical” definition of Cardiotoxicity.....
Beyond Type I and Type II cardiotoxicity !!

- Type I: Anthracyclines
- Type II: HER2 inhibitors
- Type III: Vascular endothelial growth factor (VEGF) inhibitors
- Type IV: Bcr-Abl inhibitors
- Type V: 5-FU and 5-FU metabolites
- Type VI: Checkpoint inhibitors
- Type VII: Proteosome inhibitors
- Type VIII: Histone deacetylase inhibitors
- Type IX: Bruton's tyrosine kinase inhibitors
- Type X... etc.
1. Prevention, Detection and Mgt of Drug induced Cardiotoxicity
2. Radiation Induced heart disease
3. Cardio-Oncological emergencies
CARDIO-ONCOLOGY : THE PREVENTION
PREVENTION OF CARDIO-TOXICITY

1. Risk stratification to identify higher risk patients
2. Early detection with biomarkers, imaging
3. Primary prevention drugs and interventions
## Risk Factors for Anthracycline Cardiotoxicity

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Hazard ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior anthracycline use (cumulative dose)</td>
<td>NA</td>
<td>Von Hoff et al. (1979)²⁷</td>
</tr>
<tr>
<td>Cardiac irradiation</td>
<td>NA</td>
<td>Steinherz et al. (1991)¹¹²</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>1.53</td>
<td>Hershman et al. (2008)¹¹³</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.58</td>
<td>Hershman et al. (2008)¹¹³</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.21</td>
<td>Hershman et al. (2008)¹¹³</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>2.25</td>
<td>Swain et al. (2003)³³</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.
EARLY DETECTION OF CARDIOTOXICITY
CLINICAL

- **Patient education is key** and awareness of signs and symptoms such as dyspnea, chest pressure, unusual weight gain, edema, worsening effort tolerance, palpitations etc should be reinforced to the patient in context of the potential cardiotoxicity of the chemo they are receiving.
EARLY DETECTION WITH BIOMARKERS
BNP trials

- Do not predict future LV dysfunction
- Poor sensitivity in detecting asymptomatic LV dysfunction
- Higher levels associated with worse prognosis & MACE
- Nt-ProBNP more sensitive
Troponin trials

- Elevated troponin I at 3 months predictive of future decline in LVEF
- But troponin level does not correlate with degree of LV dysfunction
- ?timing of drawing troponin
EARLY DETECTION WITH ECHO
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

Juan Carlos Plana, MD, FASE, Chair, Maurizio Galderisi, MD, FESC, Co-Chair, Ana Barac, MD, PhD, Michael S. Ewer, MD, JD, Bonnie Ky, MD, FASE, Marielle Scherrer-Crosbie, MD, PhD, FASE, Javier Ganame, MD, PhD, FASE, Igal A. Sebag, MD, FASE, Deborah A. Agler, RCT, RDCS, FASE, Luigi P. Badano, MD, PhD, FESC, Jose Banchs, MD, FASE, Daniela Cardinale, MD, PhD, FESC, Joseph Carver, MD, Manuel Cerqueira, MD, Jeanne M. DeCara, MD, FASE, Thor Edvardsen, MD, PhD, FESC, Scott D. Flamm, MD, MBA, Thomas Force, MD, Brian P. Griffin, MD, Guy Jerusalem, MD, PhD, Jennifer E. Liu, MD, FASE, Andrea Magalhães, MD, Thomas Marwick, MBBS, PhD, MPH, Liza Y. Sanchez, RCS, FASE, Rosa Sicari, MD, PhD, FESC, Hector R. Villarraga, MD, FASE, and Patrizio Lancellotti, MD, PhD, FESC, Cleveland, Ohio; Naples, Padua, Milan, and Pisa, Italy; Washington, District of Columbia; Houston, Texas; Philadelphia, Pennsylvania; Boston, Massachusetts; Hamilton, Ontario and Montreal, Quebec, Canada; Chicago, Illinois; Oslo, Norway; Liege, Belgium; New York, New York; Lisbon, Portugal; Hobart, Australia; Rochester, Minnesota

(J Am Soc Echocardiogr 2014;27:911-39.)

Keywords: Chemotherapy, Doxorubicin, Trastuzumab, Left ventricular dysfunction, Three-dimensional echocardiography, Early detection, Strain, Biomarkers
Cardiotoxicity or CTRCD

- ASE definition * of Cancer Therapeutics–Related Cardiac Dysfunction (CTRCD):
  1. A decrease in the LVEF of >10 %
  2. To a value <55% [ or the LLN of your lab]

Mayo clinic /ESMO/ASE guidelines for Anthracycline cardiac monitoring

- **Initial evaluation**
  - **LVEF >50%**
    - Initiation of anthracycline therapy
    - Reassessment at 250-300 mg/kg²
      - No high risk
        - Reassessment before each cycle
      - High risk
        - Reassessment at 450 mg/kg²
        - Reassessment before each cycle
        - Discontinue if LVEF ↓ ≥10% and LVEF ≤50%
  - **LVEF <50%**
    - Reassessment before each cycle
    - Discontinue if LVEF ↓ ≥10% or LVEF ≤30%
Mayo clinic /ESMO/ASE guidelines for Trastuzumab cardiac monitoring
But there is a problem with LVEF!!!

1. We don’t do a good job of measuring LVEF
2. LVEF is a late manifestation of cardiotoxicity
Conclusion: Overall, non contrast 3DE also had the best intra- and inter-observer as well as test-retest variability, being the most reproducible technique for LVEF and LV volume measurements over 1 year of follow-up in patients undergoing chemotherapy.
The 2nd Problem with LVEF: It Occurs Late!!

- A decrease in longitudinal strain from baseline to 3 months and hs- Tn I at 3 months were the BEST independent predictors of the development of cardiotoxicity at 6 months.

- The LVEF, parameters of diastolic function, and NT-BNP did not predict cardiotoxicity

*Sawaya et al Am J Cardiol 2011;Mar 7*
What is strain?

- *Strain* denotes percentage thickening or deformation of the myocardium during the cardiac cycle.
- Strain can be: Radial, longitudinal, circumferential, and transversal strain.
Strain rate imaging by Speckle tracking echocardiography [STE]

A= LONGITUDINAL STRAIN

B = RADIAL STRAIN

C= CIRCUMFERENTIAL STRAIN

Speckles’ are small dots or groups of myocardial pixels that are routinely created by the interaction of ultrasonic beams and the myocardium. They have specific gray scale characteristics or signature, and the ability to identify and track the same speckle throughout the cardiac cycle by 2D echocardiography forms the basis for 2D STE.
Longitudinal strain: Is the shortening of ventricular length as the base moves towards the apex during systole. The figure on the left denotes end-diastole and the one on the right depicts end-systole. Note the downward descent of the mitral annulus toward the apex in systole. There is a reduction in length by 2 cm, which is a 25% decrease. As there is a decrease in the longitudinal length, it will be denoted by a negative (−) sign; hence the longitudinal strain will be −25%
Global Longitudinal Strain [GLS]

• All strain parameters can be individualized for each of the myocardial segments or can be expressed as Global longitudinal Strain [GLS] when all the segmental values are averaged.
Use of Myocardial Strain Imaging by Echocardiography for the Early Detection of Cardiotoxicity in Patients During and After Cancer Chemotherapy

A Systematic Review

Paaladinesh Thavendiranathan, MD,*† Frédéric Poulin, MD,* Ki-Dong Lim, MD,* Juan Carlos Plana, MD,‡ Anna Woo, MD,* Thomas H. Marwick, MD.§

Toronto, Ontario, Canada; Cleveland, Ohio; and Hobart, Australia

The literature exploring the utility of advanced echocardiographic techniques (such as deformation imaging) in the diagnosis and prognostication of patients receiving potentially cardiotoxic cancer therapy has involved relatively small trials in the research setting. In this systematic review of the current literature, we describe echocardiographic myocardial deformation parameters in 1,504 patients during or after cancer chemotherapy for 3 clinically-relevant scenarios. The systematic review was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the EMBASE (1974 to November 2013) and MEDLINE (1946 to November 2013) databases. All studies of early myocardial changes with chemotherapy demonstrate that alterations of myocardial deformation precede significant change in left ventricular ejection fraction (LVEF). Using tissue Doppler-based strain imaging, peak systolic longitudinal strain rate has most consistently detected early myocardial changes during therapy, whereas with speckle tracking echocardiography (STE), peak systolic global longitudinal strain (GLS) appears to be the best measure. A 10% to 15% early reduction in GLS by STE during therapy appears to be the most useful parameter for the prediction of cardiotoxicity, defined as a drop in LVEF or heart failure. In late survivors of cancer, measures of global radial and circumferential strain are consistently abnormal, even in the context of normal LVEF, but their clinical value in predicting subsequent ventricular dysfunction or heart failure has not been explored. Thus, this systematic review confirms the value of echocardiographic myocardial deformation parameters for the early detection of myocardial changes and prediction of cardiotoxicity in patients receiving cancer therapy. (J Am Coll Cardiol 2014;63:2751–68) © 2014 by the American College of Cardiology Foundation
Detection of early cardiotoxicity during cancer chemotherapy with strain

• 2014 Meta analysis of 30 peer reviewed studies of anthracycline cardiotoxicity:

1. All showed that a decrease in longitudinal myocardial strain occurs earlier than a decrease in LVEF

2. A fall in GLS or Global Strain by STE > 15% predicts subsequent cardiotoxicity (including both asymptomatic and symptomatic LV dysfunction

3. A value of > -18% GLS at baseline is generally normal, <16% is definitely abnormal
Transthoracic Echocardiogram

PROCEDURE(S)

- Complete two-dimensional echocardiogram (TTE)
- Color-flow imaging
- Complete Doppler

DIAGNOSES

- prior chemotherapy, right breast cancer (female)

REASON(S) FOR TESTING

- evaluate valves and ventricular function

CONCLUSIONS

- normal left ventricular size
- overall mild decreased left ventricular systolic function (diffuse); ejection fraction = 49%
- Global Longitudinal Strain: abnormal = -14.6% (Phillips)
- technically difficult study
- probable normal right ventricular size
- probable normal right ventricular function
- minimal mitral regurgitation
- minimal tricuspid regurgitation
- inadequate tricuspid regurgitation to assess right ventricular pressure
Global Longitudinal Score before and after treatment with Trastuzumab

Bull’s-eye plot showing GLS of a patient: (A) GLS and regional longitudinal strain at baseline. (B) GLS and regional longitudinal strain 3 months during trastuzumab-based therapy after anthracyclines. GLS has decreased from -20.6% to -14.4% (30% decrease). The decrease in GLS is therefore considered of clinical significance (>15% vs baseline)
This drop in GLS predicts early cardiotoxicity even before the LVEF falls.
GLS [Global Longitudinal strain] is your crystal ball for future cardiotoxicity!!
But why is GLS/strain so sensitive vs LVEF?

1. Picks up regional pattern of cardiotoxicity earlier

2. Lower inter-observer variability

3. Chemo causes subendocardial damage which affects Longitudinal LV mechanics first and hence picked up by longitudinal strain imaging first.
The potential hemodynamic burden of other tyrosine kinase inhibitors (sunitinib, sorafenib) should be considered in patients with known CAD and should be assessed according to perceived individual risk with appropriate close monitoring and treatment of blood pressure and symptoms in patients at high cardiovascular risk. In the absence of data, we recommend a baseline echocardiographic evaluation, with follow-up at 1 month and every 3 months while on therapy with VEGF or VEGF receptor inhibitors.

B. Detection of Subclinical LV Dysfunction

During chemotherapy, patients are longitudinally followed for evidence of CTRCD or subclinical LV dysfunction (abnormal GLS [Figure 16] or elevated troponins [Figure 17]). With these changes, a cardiology consultation should be considered, with discussion between the cardiologist and oncologist as to whether to continue the agent, alter the regimen, and/or consider the initiation of cardioprotective agents.

The ideal strategy for the detection of subclinical LV dysfunction is to compare the measurements of GLS obtained during chemotherapy with the one obtained at baseline, allowing the patient to serve as his or her own control. A relative percentage reduction in GLS of >15% is very likely to be abnormal, whereas a change of <8% appears not to be of clinical significance (Figures 9a and 9b). The abnormal GLS value should be confirmed by a repeat study. The repeat study should be performed 2 to 3 weeks after the initial abnormal study.

When comparing LV EF and GLS values, it is essential to keep in mind the load dependency of these measurements. This committee recommends reporting the timing of the echocardiographic examination with respect to the intravenous infusion of chemotherapeutic agents (number of days before or after treatment) as well as the vital signs measured during the test (blood pressure and heart rate), recognizing that changes in loading conditions are frequent and may affect the GLS value (volume expansion due to the intravenous administration of chemotherapeutic agents or volume contraction due to vomiting or diarrhea).

Troponin levels are measured before and/or 24 hours after each chemotherapy cycle. Patients with troponin elevations during therapy (as defined by the cutoffs specific to the assay platform used in the individual labs) are at a higher risk for subsequent cardiovascular events. As such, it is suggested to obtain a cardiology consultation.

Troponin levels have added prognostic value to GLS. If both are abnormal, the specificity for the prediction of CTRCD increases from 73% to 93%. If both are normal, the negative predictive value increases to 91%.

An elevation in NT-proBNP raises concern for increased LV filling pressures in the setting of CTRCD. The negative predictive value of NT-proBNP may be useful, but the variability over time has limited its utility. Further studies in this area are needed.

It is the recommendation of this committee to consider the use of CMR in situations in which discontinuation of chemotherapeutic regimens secondary to CTRCD is being entertained or when, because of technical limitations or the quality of echocardiographic images, the estimation of the LV EF is thought to be controversial or unreliable.

Although small studies suggest the role of the initiation of cardioprotective regimens in the setting of subclinical LV dysfunction, there is a lack of conclusive data (randomized clinical trials) supporting this strategy.

If the agent is continued despite LV functional changes, reassessment should be undertaken by imaging, ideally with GLS and/or troponins before each additional cycle, with the understanding that the risk for cardiac events...
For doses > 240 mg/m², measurements of LVEF, GLS, and troponin are recommended before each additional 50 mg/m².
MONITORING TYPE II CARDIOTOXICITY

- Initiation of trastuzumab
  - Baseline evaluation of LVEF
    - 3DE (preferred) / 2DE (consider contrast)
      - GLS or Troponin I
  - LVEF < 53%
    - GLS < LLN**
      - + Troponins
        - Cardiology consultation
  - LVEF > 53%
    - GLS > LLN**
      - - Troponins
        - 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.
PREVENTION OF CARDIOTOXICITY
Prevention of Cardiotoxicity

1. **Pre –chemo Risk Assessment and Treat cardiac risk factors** such as CAD and HTN
2. **Change drug or dose**: Weigh and balance the risks vs benefits
3. **Change Infusion regimen**: Increase the length of infusion instead of bolus infusions [such as with 5FU and anthracyclines]
4. **Use protective therapies**: DEXRAZOXANE
5. **Switch dosage forms**: liposomal formulation of doxorubicin: DOXIL which has less toxicity
6. **Use fewer cardio toxic agents in combination therapy** eg using docetaxel instead of paclitaxel along with Doxo/transtuzumab based regimens
7. **Primary prevention of LV dysfunction** with ACE-I and beta blockers
Prevention: Alter Risk Factors for Anthracycline Cardiotoxicity

<table>
<thead>
<tr>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative dose</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>- &gt;65 years old</td>
</tr>
<tr>
<td>- Paediatric population (&lt;18 years)</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Concomitant or previous radiation therapy involving the heart</td>
</tr>
<tr>
<td>Concomitant chemotherapy</td>
</tr>
<tr>
<td>- alkylating or antimicrotubule agents</td>
</tr>
<tr>
<td>- immuno- and targeted therapies</td>
</tr>
<tr>
<td>Pre-existing conditions</td>
</tr>
<tr>
<td>- Cardiac diseases associating increased wall stress</td>
</tr>
<tr>
<td>- Arterial hypertension</td>
</tr>
<tr>
<td>- Genetic factors</td>
</tr>
</tbody>
</table>

PREVENTION OF CARDIO TOXICITY: Alternative regimens

<table>
<thead>
<tr>
<th>Agent</th>
<th>Relative Cardiotoxicity</th>
<th>Maximum Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bolus</td>
<td>1</td>
<td>400</td>
</tr>
<tr>
<td>• Weekly</td>
<td>0.7</td>
<td>550</td>
</tr>
<tr>
<td>• 24 hr infusion</td>
<td>0.64</td>
<td>550</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>0.75</td>
<td>800</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>0.53</td>
<td>150</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>0.66</td>
<td>900</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>0.5</td>
<td>160</td>
</tr>
</tbody>
</table>
PREVENTION OF CARDIOTOXICITY: AVOID HIGHER CUMULATIVE DOSES!!

<table>
<thead>
<tr>
<th>* DOSE</th>
<th>Incidence of cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300 MG/M2</td>
<td>MINIMAL BUT POSSIBLE</td>
</tr>
<tr>
<td>400-450 MG /M2</td>
<td>5%</td>
</tr>
<tr>
<td>550 MG/M2</td>
<td>7-26%</td>
</tr>
<tr>
<td>700 MG/M2</td>
<td>18-48%</td>
</tr>
</tbody>
</table>

* FOR DOXORUBICIN
Prevention: Change Infusion regimens

1. Weekly regimens of doxo < cardiotoxic than 3 weekly bolus doses without affecting oncological benefit
2. 72 hour doxo infusional pumps less cardiotoxic vs 20 minute infusions
3. Oral busulfan not cardiotoxic like IV busulfan is
4. 5FU boluses may be preferred to long 5FU infusions in patients with cardiotoxicity /vasospasm
Using Cardioprotectants: DEXRAZOXANE

- Iron chelator but that’s NOT mechanism of action as thought earlier
- Reduces anthracycline cardiotoxicity with a RRR of 79%
- In some earlier adult studies showed causing myelosuppression, secondary leukemia, decreased drug efficacy, so use is limited
- In the USA it is approved only for adult patients who had ALREADY received >300 mg/m2 dose and needed additional anthracyclines
Dexrazoxane mechanism of preventing Anthracycline cardiotoxicity

- Dexrazoxane binds with and inhibits anthracyclines from binding with Topo2b
- Therefore Topo2b-Doxo mediated DNA double strand breaks don’t occur, preventing cardiotoxicity
- Patients who developed AC cardiotoxicity had higher levels of topo2b
- Measuring topo2B levels emerging field to consider using Non AC regimens or to use preemptive protection with dexrazoxane
Anthracycline Cardiotoxicity: Effects of Different Drugs, Scheduling, and Cardiac Protection with Dexrazoxane

- Epirubicin 1000 mg/m²: 15 CHF (%)
- Epirubicin < 900 mg/m²: 4 CHF (%)
- Dauno 1000 mg/m²: 12 CHF (%)
- Dauno 500 mg/m²: 1.5 CHF (%)
- Doxo (400-499 mg/m²) + Dexrazoxane: 1 CHF (%)
- Doxo low dose weekly > 600 mg/m²: 5.4 CHF (%)
- Doxo bolus > 550 mg/m²: 10 CHF (%)
- Doxo 1000 mg/m²: 20 CHF (%)
- Doxo 500 mg/m²: 7 CHF (%)

Hensley ML et al J Clin Oncol 1999; 17(10):3333-3355
Prevention: Switch dosage forms

• **DOXIL [liposomal doxorubicin]**: Liposomal delivery systems increases size of drug molecule, which is able to penetrate into the immature larger vascular beds of the tumor but not into the the heart via its normal vasculature.

• It is approved for ovarian CA, multiple myeloma, Kaposi’s sarcoma, metastatic Breast Ca and lymphoma

• Allows twice the number of cycles to be given compared to Doxo, with similar oncological benefit in some cancers
ACE-I AND BETA BLOCKERS

• Primary prevention of cardiotoxicity
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Cohort</th>
<th>F/u time</th>
<th>Cardiotoxic chemotherapy</th>
<th>Radiation therapy</th>
<th>Preventive therapy</th>
<th>Cardiotoxicity definition</th>
<th>Outcome with vs without previous therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trials, continued</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nakamara et al. (2005)</td>
<td>2005</td>
<td>NHL (n=40)</td>
<td>Day 3</td>
<td>CHOP</td>
<td>0%</td>
<td>Valasartan 80 mg/d, administered and continued with CT</td>
<td>LVEDD (mm)</td>
<td>45 vs 49&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dessi et al. (2011)</td>
<td>2011</td>
<td>Various (n=49, breast cancer 37%)</td>
<td>12 mo</td>
<td>Epirubicin 400 mg/m²</td>
<td>0%</td>
<td>Telmisartan 40 mg/d, administered</td>
<td>BNPI (pmol/L)</td>
<td>30 vs 80&lt;sup&gt;o&lt;/sup&gt;</td>
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<tr>
<td>Acar et al. (2011)</td>
<td>2011</td>
<td>Various (n=40)</td>
<td>6 mo</td>
<td>Anthracyclines: doxorubicin 256 mg/m²; idarubicin 297 mg/m²</td>
<td>NA</td>
<td>Atorvastatin 40 mg/d, administered before and continued for 6 mo after CT</td>
<td>Strain rate</td>
<td>420 vs 435&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bosch et al. (OVERCOME trial)</td>
<td>2013</td>
<td>Acute leukemia (n=36) or HSCT (n=54)</td>
<td>6 mo</td>
<td>Anthracyclines: (40% before, 40% during, cumulative 265 mg/m²)</td>
<td>18%</td>
<td>Carvedilol (625-25 mg BID) and enalapril (2.5-10 mg BID), administered 24 h before CT and continued in f/u</td>
<td>LVEF (%), absolute change by TTE</td>
<td>1.3 vs −7.9&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Silver et al. (AAA study)</td>
<td>2004</td>
<td>Pediatric cancer survivors with ≥1 cardiac abnormalities in f/u (n=135)</td>
<td>35 mo</td>
<td>Anthracyclines 300 mg/m²</td>
<td>36%</td>
<td>Enalapril 0.05-0.15 mg/kg per d</td>
<td>LVEF (%), absolute change by CMR imaging</td>
<td>−0.15 vs 2.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardinale et al. (2006)</td>
<td>2006</td>
<td>HDC (n=114, 60% NHL and breast cancer + cTnI &gt;ULN within 3 d of any cycle)</td>
<td>12 mo</td>
<td>Various, cumulative doxorubicin equivalent dose 335 mg/m²</td>
<td>11%</td>
<td>Enalapril 2-20 mg/d, administered after cTnI elevation and continued in f/u</td>
<td>LVEF decrease &gt;10% to &lt;50% rate (%)</td>
<td>0 vs 43&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Interaction term (change due to treatment) <sup>P=.84</sup>
<sup>b</sup> Interaction term (change due to treatment) <sup>P=.28</sup>
<sup>c</sup> Interaction term (change due to treatment) <sup>P=.55</sup>
# BETA BLOCKER TRIALS

## TABLE 2. Adjunctive Pharmacological Strategies for the Prevention of Chemotherapy-Induced Cardiotoxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Cohort</th>
<th>F/u time</th>
<th>Cardiotoxic chemotherapy</th>
<th>Radiation therapy</th>
<th>Preventive therapy</th>
<th>Cardiotoxicity definition</th>
<th>Outcome with vs without previous therapy</th>
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</thead>
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<tr>
<td>Randomized controlled trials</td>
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<tr>
<td>Kalay et al. (26) 2006</td>
<td>2006</td>
<td>Breast cancer (68%), lymphoma (18%)</td>
<td>6 mo</td>
<td>Anthracyclines: doxorubicin 520 mg/m² or epirubicin 780 mg/m²</td>
<td>0%</td>
<td>Carvedilol 12.5 mg/d, administered before CT and continued for 6 mo</td>
<td>LVEF (%)</td>
<td>Carvedilol: no change; Control: significant decrease (68.9-52.3)</td>
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<tr>
<td>El-Shitany et al. (26 2012</td>
<td>2012</td>
<td>Children with ALL (n=50)</td>
<td>1 wk after CT</td>
<td>Doxorubicin 120 mg/m²</td>
<td>0%</td>
<td>Carvedilol 0.1-1 mg/d, administered 5 d before CT</td>
<td>FS (%)</td>
<td>39.5±6.3 vs 33.5±6.2&lt;sup&gt;a&lt;/sup&gt; -19.3±2.0 vs -15.1±1.8&lt;sup&gt;b&lt;/sup&gt; 0.02±0.02 vs 0.06±0.05&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Eltik et al. (27) 2013</td>
<td>2013</td>
<td>Breast cancer (n=80)</td>
<td>6 mo</td>
<td>Anthracyclines 520 mg/m²</td>
<td>0%</td>
<td>Carvedilol 12.5 mg/d, administered before CT and continued for 6 mo</td>
<td>Peak systolic strain, septal (%)</td>
<td>20±5.3 vs 16±4.3&lt;sup&gt;a&lt;/sup&gt; 18±5.6 vs 14±6.1&lt;sup&gt;b&lt;/sup&gt; 64±5.1 vs 63±4.8</td>
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<tr>
<td>Kaya et al. (26) 2012</td>
<td>2012</td>
<td>Breast cancer (n=45)</td>
<td>6 mo</td>
<td>Anthracyclines: doxorubicin 246 mg/m² or epirubicin 354 mg/m²</td>
<td>27%</td>
<td>Nebivolol 5 mg/d, administered 7 d before CT and continued for 6 mo</td>
<td>LVEF (%)</td>
<td>63.8±3.9 vs 57.5±5.6&lt;sup&gt;a&lt;/sup&gt; 152±69 vs 204±73&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Georgakopoulos et al. (26) 2010</td>
<td>2010</td>
<td>HL and NHL (n=125)</td>
<td>12 mo</td>
<td>ABVD R-CHOP</td>
<td>21%</td>
<td>Metoprolol 25-50 mg BID or enalapril 2.5-10 mg BID, administered with CT</td>
<td>New HF rate (%)</td>
<td>2.4 or 4.7 vs 0 (P=.56)</td>
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<tr>
<td>Bosch et al. (OVER-COME trial) 2013</td>
<td>2013</td>
<td>Acute leukemia (n=36) or HSCT (n=54)</td>
<td>6 mo</td>
<td>Anthracyclines (40% before, 40% during, cumulative 265 mg/m²)</td>
<td>18%</td>
<td>Carvedilol (6.25-25 mg BID) and enalapril (2.5-10 mg BID), administered 24 h before CT and continued in f/u</td>
<td>LVEF (%), absolute change by -0.17 vs -3.28&lt;sup&gt;c&lt;/sup&gt; TTE</td>
<td>LVEF (%), absolute change by 0.36 vs -3.04 (P=.09) CMR imaging</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> Significant difference from the control group at a significance level of P<.05.

<sup>b</sup> Significant difference from the control group at a significance level of P<.01.

<sup>c</sup> Significant difference from the control group at a significance level of P<.001.
Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (prevention of left ventricular dysfunction with Enalapril and carvedilol in patients submitted to intensive Chemotherapy for the treatment of Malignant Hemopathies)

Xavier Bosch, MD, PhD,*↑ Montserrat Rovira, MD, PhD,↑↑ Marta Sitges, MD, PhD,*↑
Ariadna Domènec, RN,↑ José T. Ortiz-Pérez, MD, PhD,*↑ Teresa M. de Caralt, MD, PhD,↑
Manuel Morales-Ruiz, PhD,↑↑↑ Rosario J. Perea, MD, PhD,↑↑ Mariano Monzó, MD, PhD,↑↑
Jordi Esteve, MD, PhD↑↑
Barcelona, Spain

Conclusions
Combined treatment with enalapril and carvedilol may prevent LVSD in patients with malignant hemopathies treated with intensive chemotherapy. The clinical relevance of this strategy should be confirmed in larger studies. (Prevention of Left Ventricular Dysfunction During Chemotherapy [OVERCOME]: NCT01110824) (J Am Coll Cardiol 2013;61:2355-62) © 2013 by the American College of Cardiology Foundation
Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Primary Results of a Randomized, 2 x 2 Factorial, Placebo-Controlled, Double-Blind Clinical Trial

Geeta Gulati¹, Siri Lagethon Heck¹, Anne Hansen Ree¹, Pavel Hoffmann², Jeanette Schulz-Menger³, Morten W Fagerland², Berit Gravdehaug¹, Florian von Knobelsdorff-Brenkenhoff³, Åse Bratland², Tryggve H Storås², Tor-Arne Hagve¹, Helge Røsjø¹, Kjetil Steine¹, Jürgen Geisler¹, Torbjørn Omland¹

¹ Akershus University Hospital, Lørenskog, Norway; ² Oslo University Hospital, Oslo, Norway; ³ Charité Campus Buch/HELIOS, Berlin, Germany
Primary results of candesartan

Effect of Candesartan

$p = 0.76$

$p = 0.47$

$p = 0.09$

$p = 0.28$

$p = 0.43$

Sample
(n=total/candesartan/not candesartan)

All patients (n=109/57/52)

Age > median (n=55/28/27)
Age ≤ median (n=54/29/25)

Current smoker (n=19/11/8)
Not current smoker (n=90/46/44)

BMI > median (n=51/20/31)
BMI ≤ median (n=58/37/21)

Trastuzumab (n=25/13/12)
No trastuzumab (n=84/44/44)

No radiation (n=24/14/10)
Left sided radiation (n=40/23/17)
Right sided radiation (n=45/20/25)
Primary results of metoprolol

Difference in change in LVEF (95% CI) from baseline to end-of-study

Sample
(n=total/metoprolol/not metoprolol)

All patients (n=109/54/55)

Age > median (n=55/25/30)
Age ≤ median (n=54/29/25)

Current smoker (n=19/8/11)
Not current smoker (n=90/46/44)

BMI > median (n=51/25/26)
BMI ≤ median (n=58/29/29)

Trastuzumab (n=25/12/13)
No trastuzumab (n=84/42/42)

No radiation (n=24/9/15)
Left sided radiation (n=40/20/20)
Right sided radiation (n=45/25/20)
Rationale and design of the Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research Trial (MANTICORE 101 - Breast): a randomized, placebo-controlled trial to determine if conventional heart failure pharmacotherapy can prevent trastuzumab-mediated left ventricular remodeling among patients with HER2+ early breast cancer using cardiac MRI

Edith Pituskin, Mark Haykowsky, John R Mackey, Richard B Thompson, Justin Ezekowitz, Sheri Koshman, Gavin Oudit, Kelvin Chow, Joseph J Pagano and Ian Paterson
Protective effects of nebivolol against anthracycline-induced cardiomyopathy: A randomized control study

Mehmet G. Kaya, Metin Ozkan, Ozgur Gunebakmaz, Hasan Akkaya, Esma G. Kaya, Mahmut Akpek, Nihat Kalay, Mustafa Dikilitas, Mikail Yarlioglu, Halit Karaca, Veli Berk, Idris Ardic, Ali Ergin, Yat Yin Lam

International Journal of Cardiology 167 (2013) 2306-2310
PREVENTATIVE ROLE OF STATINS?

STOP –CA trial
SPARE-HF trial
Figure Legend:

Heart Failure-Free Survival
These survival curves illustrate survival in statin (red) and non-statin (blue) treated groups. Figures above the abscissa relate to numbers of patients surviving without heart failure at each 12-month interval.
Early Intervention for Cardiotoxicity
Early treatment is key!

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

- 1-2 months: 64% (n=75)
- 2-4 months: 28% (n=35)
- 4-6 months: 7% (n=20)
- 6-8 months: 0% (n=12)
- 8-10 months: 0% (n=8)
- 10-12 months: 0% (n=7)
- >12 months: 0% (n=44)

Recovery of LV dysfunction with standard HF therapy

BUT THE MECHANISM OF CTRCD OR CHF FROM CHEMOTHERAPEUTICS IS NOT THE SAME
<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Incidence (%)</th>
<th>Frequency of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthracyclines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin)</td>
<td>3–26*</td>
<td>+++</td>
</tr>
<tr>
<td>Epirubicin (Ellence)</td>
<td>0.9–11</td>
<td>++</td>
</tr>
<tr>
<td>Idarubicin (Idamycin PFS)</td>
<td>5–18</td>
<td>+</td>
</tr>
<tr>
<td><strong>Alkylating agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide (Cytoxan)</td>
<td>7–28</td>
<td>+++</td>
</tr>
<tr>
<td>Ifosfamide (Ifex)</td>
<td>17</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
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<tr>
<td>Clofarabine (Clolar)</td>
<td>27</td>
<td>+</td>
</tr>
<tr>
<td><strong>Antimicrotubule agents</strong></td>
<td></td>
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<tr>
<td>Docetaxel (Taxotere)</td>
<td>2.3–13</td>
<td>++</td>
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<tr>
<td><strong>Monoclonal antibody-based tyrosine kinase inhibitors</strong></td>
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<tr>
<td>Bevacizumab (Avastin)</td>
<td>1.7–4</td>
<td>++</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>2–28</td>
<td>++</td>
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<tr>
<td><strong>Proteasome inhibitor</strong></td>
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<tr>
<td>Bortezomib (Velcade)</td>
<td>2–5</td>
<td>++</td>
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<tr>
<td>Carfilzomib</td>
<td>11–25</td>
<td>+++</td>
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<tr>
<td><strong>Small molecule tyrosine kinase inhibitors</strong></td>
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<tr>
<td>Dasatinib (Sprycel)</td>
<td>2–4</td>
<td>++</td>
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<tr>
<td>Imatinib mesylate (Gleevec)</td>
<td>0.5–1.7</td>
<td>+</td>
</tr>
<tr>
<td>Lapatinib (Tykerb)</td>
<td>1.5–2.2</td>
<td>+</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>2.7–19</td>
<td>+++</td>
</tr>
</tbody>
</table>

Dr Coleman’s Case

- 75 year old physician with non small cell CA lung treated with Keytruda [pembrolizumab] admitted with sudden SOB [ PE vs CAD vs his lung Cancer]
- Troponin 36, new anterior T wave inversions and Q waves
- PE ruled out with CTA. Lung Cancer stable.
- Cath normal coronaries
- Echo new decline in EF 35%
- Goes into subsequent complete heart block
New immunotherapy drug behind Jimmy Carter's cancer cure

Former president given pembrolizumab, one of the most promising new drugs in the treatment of cancer.
Fulminant Myocarditis with Combination Immune Checkpoint Blockade

- Nov 2016 NEJM
- 2 mortality cases from checkpoint inhibitors Nivolumab and Ipilimumab
- Acute CHF due to immune mediated myocarditis from ICI’S
Dr Coleman’s case

- 2 mg/kg methylprednisolone
- Recovery of LVEF from 35% to 45% with improvement in symptoms
- Heart block does not recover, needs PPM
- Discharged home on standard heart failure therapy and continued tapering steroids for a month
- In home hospice but in “good spirits”
Myocarditis by ICI’s is more common than reported [upto 1.14%], without a decline in LVEF by echo

- Occurs mostly in first 3 months [34 days median time]
- Mostlly with PD-1 inhibitors such as Pembrolizumab and Nivolumab
- Troponin I and EKG best tools for detection [abnormal in 94% & 89% pts respectively with myocarditis]
- Worse MACE if trop>1.5
- Treatment is high dose steroids
- Question of re-challenge unanswered
Takotsubo Very Common in Cancer Patients

A Mechanism of Presumed Cardiotoxicity?

Stress-Induced Cardiomyopathy in Cancer Patients

Long-term prognosis of the transient left ventricular dysfunction syndrome (Tako-Tsubo cardiomyopathy): Focus on malignancies

Dana Elena Giza, MD, Juan Lopez-Munoz, MD, Piparadeepongsit, MD, Ezequiel Munoz, MD, Gloria Hiescu, MD, Dana Kungyan, MD, S.B. Hassan, MD, Peter Kim, MD, Miha S. Ewer, MD, Cezar Hiescu, MD

Takotsubo-Like Syndrome in Cancer Patients Treated With Immune Checkpoint Inhibitors

European Journal of Heart Failure 10 (2008) 1005–1019

European Journal of Heart Failure 10 (2008) 1005–1019
OTHER CARDIOTOXICITY

- Ischemia
- Arterial hypertension
- Thrombo-embolism
- Bradycardia
- QT prolongation
- Atrial fibrillation and arrhythmias
- Pericardial effusion/Pericarditis
- Radiation’s cardiac effects
**Table 2** ‘Cardiotoxicity’ of common cancer therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>LVSD</th>
<th>HTN</th>
<th>Angina</th>
<th>ACS</th>
<th>Takotsubo</th>
<th>Stroke</th>
<th>PAD</th>
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</tbody>
</table>
Chemo causing ischemia

- Fluorouracil (5-FU; Adrucil)
- Bevacizumab (Avastin)
- Capecitabine (Xeloda)
- Docetaxel (Taxotere) and Paclitaxel (Taxol)
- Erlotinib (Tarceva)
- Sorafenib (Nexavar)
- Sunitinib (Sutent)
- Lapatinib (Tykerb)
- Pazopanib (Votrient)
- Cytarabine (Depocyt)
- Ifosfamide (Ifex)
- Cisplatin
ACS in cancer patients [caveats]

- **Thrombocytopenia** does not protect cancer patients from ischemic heart ds. Long term DAPT safe in moderate >50k thrombocytopenia
- Use **radial approach** for cath to reduce bleeding
- Decision for BMS vs DES if high bleeding risk, but higher risk of ISR in BMS if h/o RT to chest
- CABG risk 3 times mortality esp if past RT, DO PCI!!
- ASA ok to use for platelets> 10 k
- Clopidogrel ok to use for 30-50 k
- Prasugrel/Ticagrelor/GPIIbIIIa platelets > 50 k and avoid due to increased bleeding risk
ACS in Cancer Patients [ACC/AHA]

Flowchart:
- ACS & Platelet < 100,000 (no active bleeding or sepsis)
  - TIMI Risk Score
    - < 3: Medical Management
      - ASA (10 K), BB, Statins followed by ischemic evaluation
    - > 3: Early Invasive Therapy - Cardiac Cath
      - CAD: Onco-cardio Team
        - ASA if PLT > 10 K
      - Stress induced CMP (Tako-Tsubo)
        - Medical Management
        - Resume Cancer Therapy in two to four weeks
<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Incidence</th>
<th>Frequency of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal antibody-based tyrosine kinase inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>4–35</td>
<td>++</td>
</tr>
<tr>
<td><strong>tyrosine kinase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>17–43</td>
<td>+++</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>5–47</td>
<td>+++</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>33-58%</td>
<td>++</td>
</tr>
<tr>
<td>Dasatinib [Sprycel]</td>
<td>6-40%</td>
<td>++</td>
</tr>
<tr>
<td>Imatinib [Gleevec]</td>
<td>10-45%</td>
<td>+++</td>
</tr>
<tr>
<td><strong>proteosome inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>10- 25</td>
<td>++</td>
</tr>
<tr>
<td>Chemotherapy Agents</td>
<td>Incidence (%)</td>
<td>Frequency of Use</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Alkylating agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin (Platinol-AQ)</td>
<td>8.5</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Angiogenesis inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide (Revlimid)</td>
<td>3–75*</td>
<td>+</td>
</tr>
<tr>
<td>Thalidomide (Thalomid)</td>
<td>1–58*</td>
<td>+</td>
</tr>
<tr>
<td><strong>Histone deacetylase inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vorinostat (Zolinza)</td>
<td>4.7–8</td>
<td>+</td>
</tr>
<tr>
<td><strong>Small molecule tyrosine kinase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>3.9–11</td>
<td>+++</td>
</tr>
</tbody>
</table>
Anticoagulation in cancer patients

- **LMWH superior to coumadin** [ CLOT NEJM 2003 with dalteparin ]
- **NOACs superior to Coumadin in VTE** [ EINSTEIN DVT /PE substudy for rivaroxaban & AMPLIFY substudy for apixaban and RECOVER for dabigatran ]
- **NOACs ??? superior to LMWH** with tendency to ess recurrent VTE [ Chest2015 meta-analysis ]
- **NOAC VS LMWH : 2 head to head trials 2018 : Hokusai VTE [NEJM]** with edoxaban vs dalteparin and **SELECT D** with rivaroxiban vs dalteparin [ less VTE but more bleeding esp with GI cancers ]
- **Therefore avoid NOACs in GI AND GU tumors**, otherwise equal to LMWH with less VTE, more bleeding.
# CHEMO CAUSING BRADYCARDIA

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Incidence (%)</th>
<th>Frequency of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide (Thalomid)</td>
<td>0.12–55%</td>
<td>+</td>
</tr>
<tr>
<td>Lenalidomide [Revlimid]</td>
<td>2–30%</td>
<td>++</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>2–10%</td>
<td>+</td>
</tr>
<tr>
<td>Paclitaxel (Taxol)</td>
<td>&lt;0.1–31%</td>
<td>++</td>
</tr>
</tbody>
</table>
# Chemotherapy Agents Causing QT Prolongation

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Incidence (%)</th>
<th>Frequency of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histone deacetylase inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vorinostat (Zolinza)</td>
<td>3.5–6</td>
<td>+</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic trioxide (Trisenox)</td>
<td>26–93*</td>
<td>+</td>
</tr>
<tr>
<td><strong>Small molecule tyrosine kinase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dasatinib (Sprycel)</td>
<td>&lt;1–3</td>
<td>++</td>
</tr>
<tr>
<td>Lapatinib (Tykerb)</td>
<td>16</td>
<td>+</td>
</tr>
<tr>
<td>Nilotinib (Tasigna)</td>
<td>1–10</td>
<td>+</td>
</tr>
</tbody>
</table>
Atrial fibrillation

• **Drugs causing AF**
  1. Anthracyclines
  2. Ibrutinib [ upto 7%] and other TKI’s
  3. Cisplatin
  4. Cyclophosphamide
  5. Gemcyctabine
  6. Melphalan
  7. IL-2
  8. Anti androgens like Abiraterone
  9. Rituximab
  10. Checkpoint inhibitors
1. **Conventional risk scores** such as the CHA2DS2-VASc score /HAS BLED not well applicable: Cancer pts have upto twice risk of thrombotic events and 2 times bleeding risk compared to non cancer patients

2. **Ibrutinib**: challenge to manage AF as causes AF and increased bleeding
   - Use rivaroxiban/apixaban or half dose dabigatran but halve dose of ibrutinib
   - Do not use coumadin, diltiazem or full dose amio with ibrutinib

3. **Consider LAA occlusion** [WATCHMAN]

4. **Careful of anticoagulation** with NOACs in GI/GU cancers
Chemo causing Pericardial Effusion

- Cyclophosphamide [Cytoxan]
- Cytarabine [Depocyt]
- Anthracyclines [Doxorubicin]
- Imatinib [Gleevec]
- Dasatinib [Sprycel]
- Interferon alpha
- Busulfan [Myelolen]
- Bortezomib [Velcade]
Radiation Induced Heart Disease
[ RIHD]
Radiation Induced Heart Disease
Radiation induced Heart disease

- **Acute** = Acute pericarditis or acute myocarditis [rare]
- **Early**: Chronic pericarditis and Constrictive pericarditis can occur in upto 20% patients **within 2 years of RT**.
- **Late**: CAD due to accelerated atherosclerosis occurs > **10 years of RT**
- **Very Late**: RT induced valve ds [ 1% at 10 yrs, 5% at 15 yrs, 6% at 20 years, > **40% at >20 years**]
ESC/ASE guidelines for RIHD

European Heart Journal – Cardiovascular Imaging (2013) 14, 721–740
doi:10.1093/ehjci/jet123

RECOMMENDATIONS

Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography
ASE recommendations for Imaging in Asymptomatic RIHD patients

1. A screening **Stress Echo for CAD** is recommended
   - At 5 years after RT in high risk patients [RR of IHD 4.2-6.7]
   - At 10 years after RT in others, and then every 2 years

2. **A screening echo for valve ds** is recommended at 10 years and then every 2 years.
Cardio-Oncological Emergencies

“No! This isn’t the place to order a blood transfusion!”
48 year asymptomatic female with routine echo surveillance after anthracyclines for metastatic breast cancer
58 year old with angiosarcoma of the liver for echo for shortness of breath
58 year old with angiosarcoma of the liver for echo for shortness of breath
Cardio-Oncology: The answered questions

1. Type I and Type 2 Cardiotoxicity

2. Cardiotoxicity: Early detection, Prevention & monitoring is key

3. Institution wide surveillance protocols should be established.

4. Awareness of non CHF cardiotoxicities

5. Radiation induced heart disease occurs late and should have echo imaging > 5-10 years even in asymptomatic individuals
CARDIO-ONCOLOGY: The Unanswered Questions

- Mechanisms of cardiotoxicity beyond Type I Type 2
- Can cardio-protective interventions therefore be uniformly applied?
- Do early indicators of cardiotoxicity such as GLS, troponin etc warrant early cardioprotective therapy? [SUCCOUR trial]
- What is the cost benefits analysis of all this surveillance?
- Does stopping or changing chemo due to cardiotoxicity translate into worse oncological outcomes?
TOO MANY MECHANISMS

- Monoclonal Antibody (mAb) or Ligand Trap
  - Given as an infusion
  - Binds ligand or receptor kinase
  - Can be covalently attached to other chemotherapy for more potency

- Multitargeted Tyrosine Kinase Inhibitor (small-molecule inhibitors)
  - Taken orally
  - Can bind more than one kinase receptor, resulting in off-target effects

- VEGF Signaling Pathway Inhibitors
  - Bevacizumab (anti-VEGF)
  - Afiblercept (VEGF trap)
  - Ranitumab (Anti-VEGFR2)

- Tyrosine Kinase Inhibitors with Anti-VEGF Activity
  - FDA Approved
    - Sunitinib, sorafenib, pazopanib, axitinib, regorafenib, vandetanib, ponatinib, cabozantinib, lenvatinib
  - Under Investigation
    - Cediranib, tirozainib, toceranib, lucitanib
Not enough in the guidelines
Not sure if it's worth the cost

Cost of Cardiac Monitoring

- Pre-Chemotherapy
- Pre-Trastuzumab
- 3 months
- 6 months
- 9 months
- 12 months

- Doxorubicin
- Cyclophosphamide
- Paclitaxel
- Trastuzumab

Every 3 weeks

- 2017 Medicare reimbursement for 2D echocardiogram = $570
- 2017 estimated new cases of invasive breast cancer = 252,710
- 2017 new cases of HER2-positive breast cancer = 63,178
- Cost of cardiac monitoring per patient = $3,420
- Cost of cardiac monitoring during BCA treatment = $216 million/yr
- Cost savings of a decrease in 1 echo per patient = $36 million/year
Pharmacogenomics and Personalized Medicine

• Understanding the mechanism of each cardiotoxic drug
• Understanding the variation in cardiotoxic response based on host genetic factors
• 54 oncological drugs have FDA approved pharmacogenomic information which can help in predicting the patients most likely to respond to a certain drug, including their susceptibility to cardiotoxicity
How are we doing at Mount Sinai’s Cardio-oncology Clinic?
CARDIO-ONCOLOGY CLINIC AT MOUNT SINAI

2. Protocols initiated for Risk Stratification, Anthracycline and Trastuzumab cardiotoxicity monitoring
3. Initiation of echo GLS protocols to detect early cardiotoxicity
4. Education of Oncology fellows, NP’s and physicians
5. Compiling registries of: cardiac amyloidosis, Carfilzomib cardiotoxicity in multiple myeloma, Checkpoint inhibitors
6. Ongoing Research projects in collaboration with Breast, Myeloma, colon cancer teams.
7. Exposure in Media: Time magazine, Cardiology Today cover article, Heme-Onc today
8. Book Chapters for Atlas of Cardio-Oncology, Hurst, Mount Sinai Expert Guides and Braunwald [upcoming]
9. Community awareness programs
The scope of our Cardio-Oncology clinic:
What we have achieved in the last year

1. 300 patient visits to Cardio-Oncology clinic in 2014
2. Facilitation of urgent imaging studies including echo, stress, CTAs and cardiac MRI’s some scheduled even the same day, helping the oncologist determine chemo regimen choices and changes
3. Coordinating and scheduling urgent same week appointments to allow prompt start of chemotherapy regimens
4. Individual follow up of test results with each patient and oncologist after imaging studies
5. Keeping registry of patients with specific disease conditions such as cardiac amyloidosis and patients undergoing Carfilzomib chemo and exhibiting cardio toxicity
6. Inpatient follow up of Cardio-oncology clinic patients when admitted
8. Research projects and abstracts: 3 separate abstracts presented in ASH, ASCO and AHA and 2 ongoing randomized trials ongoing in collaboration with the Division of Oncology

Vasoactive Action of Carfilzomib, a New Proteasome Inhibitor, on Coronary Resistance, Vascular Tone and Vascular Reactivity

Tiziano Scarabelli, MD, PhD; Carol Chen-Scarabelli, PhD; Louis Saraciatlz, MD; Riccardo Raddino, MD; Gagan Sahni, MD; Jagat Narula, MD, PhD

Mount Sinai Medical Center, New York, NY, USA; 2St John Hospital, Wayne State University, Detroit, MI, USA; 3VA Ann Arbor Healthcare System, University of Michigan, Ann Arbor, USA; 4University of Brescia, Brescia, Italy

CFZ administered in the perfusate to the isolated heart did not substantially modify left ventricular pressure (LVP) and heart rate (HR), whereas coronary perfusion pressure (CPP) was only slightly increased at the highest concentration used (from 65.2 +/- 4.1 to 78.6 +/- 8.3 mm Hg; p<0.05) (Figs. 1-2). Conversely, administration of CFZ by pulse injection caused a significant increase in CPP at all concentrations used (all p<0.05) and a mild, though significant, rise in LVP and HR at the highest concentration (Fig. 3-4). Carfilzomib administered directly into the organ bath significantly increased the basal tone of the isolated aortic strips (e.g. 0.58 +/- 0.04 at 10-7 mol/L) with plateau of contraction reached after 10 minutes (all p<0.05). Such spasmodic effect was basically doubled following ablation of the endothelium (Fig. 5). Pretreatment with CFZ for 80 minutes significantly amplified the vasoactive action exerted by 3 different agents, i.e. KCl, noradrenaline (NA) and angiotenina II (A), on aortic strips; and impaired vasodilatation following administration of nitroglycerin (NTG) and nifedipine (NFP) on the plateau of contraction induced by KCl, NA and A (all p<0.05) (Figs. 6-7). Likewise, aortic strips pretreated with CFZ exhibited impaired relaxation, as compared to untreated strips, following administration of acetylcholine (Ach), an endothelium-dependent vasodilating agent, on the plateau of NA contraction (p<0.05) (Fig. 8).

Conclusions

CFZ increased CPP, resting vasoconstricting tone and the spasmodic effect of different agents. Preincubation with CFZ decreased the anti-spasmodic activity of NTG and NFP, as well as reduced by over 50% the vasodilatory effect of Ach, suggesting that CFZ can impair vasodilation via an endothelium dependent mechanism. Further studies are warranted to establish its clinical safety in patients with known CAD and prior history of coronary spasm.

Disclosures: All authors have nothing to disclose, no conflicts of interest.
CHAPTER 101

THE DIAGNOSIS AND MANAGEMENT OF CARDIOVASCULAR DISEASE IN PATIENTS WITH CANCER

Gagan Sahni, Tiziano Scarabelli, and Edward T.H. Yeh
So what do you need to practice Cardio-Oncology?!

1. Ability

2. Affability

3. Accessibility
Hopefully this roadmap helps!! Thank you!