The Expanding spectrum of Cardio-Oncology:
Heart disease in the cancer patient
Cancer treatment related cardiotoxicities

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No Conflict of Interest Disclosures
Will Discuss off label uses
“AN IDEA IS SALVATION BY IMAGINATION”

Frank Lloyd Wright
CV Med Cardiooncology Team

➢ Dawn Piper RN

➢ Zubair Shah MD

➢ Jill Tibke APRN

➢ Charles Porter MD, Medical Director
Goals for this presentation

➢ Maintain your attention
   ❖ Send <3 texts
   ❖ Check email<3x
   ❖ No checking newsfeeds or Facebook
   ❖ Twitter just once about Conference

➢ Recall **3 facts** from this talk on Monday such as
   ❖ New cancer therapies
   ❖ New approached to preventing/managing cardiac toxicities
   ❖ CV risks in cancer survivors
   ❖ Cardiac therapies in cancer patients

➢ On Monday, email your **3 facts** to cbporter@kumc.edu
Coverage today

➢ New cancer therapies that improve cancer survival but create new cardiac toxicities

➢ Minimizing cardiac toxicities while optimizing cancer treatment outcomes: New and established therapies

➢ Impact of cancer and cancer treatment on
  ❖ Cardiovascular risk factors
  ❖ CV prognosis

➢ Assessing and managing CV risks and disease in cancer patients and survivors

➢ Acute cardiac complications of cancer
Traditional Cancer Chemotherapy versus Targeted therapy mechanisms of interrupting tumor growth

Traditional Chemo: Cancer cell growth interrupted at specific points in cell cycle along with healthy cells using same pathways create broad array of side effects related to inhibition of cell growth and recovery.

Targeted therapies: neutralize specific cell mutations that promoted uncontrolled cell growth, invasion and metastasis.

❖ Same mutation may promote carcinogenesis for different cancers.
2019: Multiple classes of anti-cancer agents with CV toxicities

**Table 1** Cancer Therapies, Cellular Targets, and Associated Cardiovascular Toxic Effects

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Cellular Target</th>
<th>Common Cardiovascular Toxic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional cancer therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>NA</td>
<td>NA</td>
<td>Mucosal ischemia, pericarditis, myocarditis, vascular heart disease, anaphylaxis</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Doxorubicin, daunorubicin, irinotecan, epirubicin, mitoxantrone</td>
<td>Type II topoisoermerase, DNA and RNA synthesis</td>
<td>Myocarditis, pericarditis, myocarditis, vascular heart disease, anaphylaxis</td>
</tr>
<tr>
<td>Platinum</td>
<td>Cisplatin, carboplatin, oxaliplatin</td>
<td>Cross-link DNA</td>
<td>Hypersensitivity, myocardial ischemia</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Fluorouracil</td>
<td>Thymidylate synthase</td>
<td>Myocardial ischemia, pericarditis, myocarditis, anaphylaxis</td>
</tr>
<tr>
<td>Aleyating agents</td>
<td>Cephalosporins</td>
<td>Thymidylate synthase</td>
<td>Myocardial ischemia, pericarditis, myocarditis, anaphylaxis</td>
</tr>
<tr>
<td>Antineoplastics</td>
<td>Paclitaxel</td>
<td>Cross-link DNA</td>
<td>Myocardial ischemia, pericarditis, myocarditis, anaphylaxis</td>
</tr>
<tr>
<td>Vinaalkoids</td>
<td>Multikinase</td>
<td>Microtubule</td>
<td>Myocardial ischemia, coronary spasm</td>
</tr>
<tr>
<td><strong>Targeted cancer therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 inhibitors</td>
<td>Trastuzumab</td>
<td>HER2</td>
<td>Decline in LVEF, congestive heart failure</td>
</tr>
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<td>Trastuzumab</td>
<td>HER2</td>
<td>Decline in LVEF, congestive heart failure</td>
</tr>
<tr>
<td>VEGF signaling pathway inhibitors</td>
<td>VEGF signaling pathway</td>
<td></td>
<td>Hypersensitivity, venous or arterial thromboembolic events, proteinuria, cardiomyopathy</td>
</tr>
<tr>
<td>VEGF trap</td>
<td>VEGF trap</td>
<td>VEGF signaling pathway</td>
<td>Hypersensitivity, venous or arterial thromboembolic events, proteinuria, cardiomyopathy</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor with anti-VEGF activity</td>
<td>Nilotinib</td>
<td></td>
<td>Pulmonary hypertension, vascular events, prolongation of QT interval corrected for heart rate</td>
</tr>
<tr>
<td>Multitargeted tyrosine kinase inhibitors</td>
<td>Dasatinib</td>
<td></td>
<td>Pulmonary hypertension, vascular events, prolongation of QT interval corrected for heart rate</td>
</tr>
<tr>
<td>Other multtargeted tyrosine kinase inhibitors</td>
<td>Crizotinib</td>
<td></td>
<td>Pulmonary hypertension, vascular events, prolongation of QT interval corrected for heart rate</td>
</tr>
</tbody>
</table>

**Table 1** Anticancer Therapies Associated With Vascular Side Effects

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Adverse Cardiovascular Effects</th>
<th>Possible Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Angina, vasospasm, MI, SC</td>
<td>Vasospasm</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Angina, vasospasm, MI, SC</td>
<td>Vasospasm</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Angina, vasospasm, MI</td>
<td>Vasospasm</td>
</tr>
<tr>
<td><strong>Antimicrotubule agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Angina, vasospasm, MI</td>
<td>Vasospasm</td>
</tr>
<tr>
<td>Vinblastine (16, 79)</td>
<td>Angina, MI</td>
<td>Endothelial injury</td>
</tr>
<tr>
<td><strong>Monoclonal antibody-based tyrosine kinase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Angina, MI, SC</td>
<td>Endothelial Injury</td>
</tr>
<tr>
<td><strong>Small molecule tyrosine kinase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Angina, vasospasm, MI</td>
<td>Vasospasm</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Angina, MI, SC</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>BCR-ABL targeted tyrosine-kinase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Angina, MI, progression of CAD, PAD</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Angina, MI, progression of CAD Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Hormone therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aromatase inhibitors (anastrozole, letrozole, exemestane)</td>
<td>Angina, MI</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone agonists (goserelin)</td>
<td>Angina, MI</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Mi indicates myocardial infarction, SC, stress-induced cardiomyopathy, CAD, coronary artery disease, PAD, peripheral artery disease.

*CTLA4 denotes cytotoxic T lymphocyte-associated protein 4, D2R dopamine receptor tyrosine kinase, FGFR fibroblast growth factor receptor, FLT3 fms-related tyrosine kinase 3, HER2 human epidermal growth factor receptor 2, IQF1 IQF1 associated protein, LVEF left ventricular ejection fraction, MEK mitogen-activated protein kinase, mTOR mammalian (or mechanistic) target of rapamycin, NA not applicable, NQO2 NADPH quinone dehydrogenase 2, PDGFR platelet-derived growth factor receptor, PI3K phosphatidylinositol 3-kinase, and VEGF vascular endothelial growth factor.

*Only two drugs targeting the PI3K-AKT-mTOR signaling pathway, everolimus and temsirolimus, which are mTOR complex 1 inhibitors, have been approved by the Food and Drug Administration. Many other inhibitors targeting this signaling pathway are currently in clinical trials.
Trastuzumab-First in class antibody targeting HER-2 receptor in breast cancer cells

➢ Rapidly developed science

❖ 1987: c-erbB-2c gene described that codes for Human Epidermal growth factor Receptor protein 2 (HER2) with intracellular tyrosine kinase activity
❖ 25% breast cancer patients HER2/neu+
❖ 1996: ASCO: HER2/neu not useful for clinical decisions
  ✴ No implications for treatment so why measure?
❖ 1998: trastuzumab (Herceptin) FDA approved as HER2/neu receptor blocker in metastatic breast cancer
Herceptin approval for HER2 positive breast cancer or metastatic gastric cancer

- September, 1998: HER2 overexpressing Metastatic Breast Cancer (MBC)
- October, 2006: HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) non-MBC
- October, 2010: Initial therapy for HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
2001: Trastuzumab improves overall survival in metastatic breast cancer

Trastuzumab Added to Chemotherapy Improves OS in MBC

- 16% HF w/ anthra + tras
- Anthra + tras not rec’d

P < 0.001

Slamon et al. NEJM 2001
Multiple drugs target HER subtypes
Trastuzumab is prototype, Lapatinib 2\textsuperscript{nd} entry, Pertuzumab, Kadcyla later to market

Anti tumor efficacies and cardiotoxicities may vary among anti HER2 agents.
20 year evolution of HER2 based therapies

Evolution of HER2 Therapy for HER2+ Breast Cancer

- **1980’s**
  - Discovery of erbB2 as an oncogenic driver of breast cancer

- **1998**
  - Trastuzumab 1st line Rx of HER2+ MBC with paclitaxel; monotherapy

- **2006**
  - Trastuzumab approved for adjuvant Rx of high risk node+ BC

- **2007**
  - Lapatinib approved for 2nd line Rx of MBC with capecitabine

- **2008**
  - Trastuzumab approved for adjuvant Rx of node+ BC

- **2012**
  - Pertuzumab approval for 1st line Rx of MBC with docetaxel and trastuzumab

- **2013**
  - Neratinib and Pertuzumab Approval for adjuvant BC

- **2017**
  - Pertuzumab Approval for neoadj BC
  - A do Trastuzumab Emtansine (T-DM1) approval for 2nd line Rx of MBC

BC = breast cancer
MBC = met breast cancer
Trastuzumab cardiac toxicity

Early Trials: Trastuzumab

- 5% develop findings LV dysfunction
- 1% develop symptomatic heart failure
- Enhanced by concurrent anthracyclines
  - Concurrent anthracycline & trastuzumab contraindicated
- Not dose dependent
- Frequently reversible
- No clinical issues with HFpEF or diastolic dysfunction
Reversibility of trastuzumab cardiotoxicity not universal

➢ Major adjuvant trastuzumab trials
  ❖ NSABP B-31
    ✴ 4.1% severe CHF, 2/3 Rx chronically for HF, 71% w/ persisting reduction EF
    ✴ 14% trastuzumab DC'd d/t decline LVEF
  ❖ BCIRG 006
    ✴ 17.3% w/ > 10% decline EF vs baseline
    ✴ 26% w/ persisting decline EF at 6 weeks off trastuzumab
  ❖ NCCTG: 29% w/ EF drop persisted at 6 months
  ❖ FinHER-No CHF or EF drop>10% after 9 weeks trastuzumab
Time course of CV events with trastuzumab

- No early peak
- Plateau seen at approximately 40 months
- Predictors of CV Event
  - Baseline EF
  - Concurrent Taxane therapy

MD Anderson experience Guarneri, J Clin Oncol 2006;24:4107
Significant reversibility reported with trastuzumab related cardiac toxicity

*resumption of trastuzumab tolerated*

MD Anderson experience 38 patients post anthracycline
Referred for trastuzumab related cardiotoxicity

- 25/38 retreated after HF Rx
- 22/25 without recurrent LV dysfunction
  - EF rise sustained
- 3/25 recurrent LV dysfx
- 13/38 No further trastuzumab
  - 7-HF Rx
  - 6-No HF Rx
  - 13/13 No further events

KU Cardio-oncology approach from 2007

- Balance risk of heart failure with risk of death from breast cancer is Cardiology/Oncology collaboration
- Advanced heart failure reported in early series with little active cardiology input
- KUH approach 2007 EF<50%: stop Herceptin, add beta blocker and ACEI inhibitor, resume at 6 weeks if echo stable or improved
  - Advance carvedilol first, then ACEI if BP tolerates
  - Monitor BNPs, clinical status but EF primary endpoint
Unpublished outcomes KU 2007-2019

- EFs persist >40%, Herceptin continued as long as 10 years in metastatic disease
- Further declines in EF uncommon, often seen with moderate hypertension
  - Advance Beta-Blocker or ACE to optimize BP
  - EFs generally recover or show stability
- Advancing disease most common indication for stopping herceptin
- No deaths or hospitalizations for HF
**SCHOLAR Trial supports KU Herceptin continuation approach**

Initiation of ACEI &/or BB If EF drop >15% or to below 50%

Open label, single arm trial

**Table A**

<table>
<thead>
<tr>
<th>Months</th>
<th>LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Enrollment</td>
<td>45</td>
</tr>
<tr>
<td>0 to &lt;3</td>
<td>45</td>
</tr>
<tr>
<td>3 to &lt;6</td>
<td>45</td>
</tr>
<tr>
<td>6 to &lt;9</td>
<td>45</td>
</tr>
<tr>
<td>9 to &lt;12</td>
<td>45</td>
</tr>
<tr>
<td>12 to &lt;24</td>
<td>45</td>
</tr>
</tbody>
</table>

**Table B**

<table>
<thead>
<tr>
<th>LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Trastuzumab</td>
</tr>
<tr>
<td>At Enrollment</td>
</tr>
<tr>
<td>On Trastuzumab</td>
</tr>
<tr>
<td>Off Trastuzumab</td>
</tr>
</tbody>
</table>


(A) Left ventricular ejection fraction (LVEF) progressively increased despite ongoing trastuzumab in individuals with mild trastuzumab cardiotoxicity when trastuzumab was accompanied by the administration of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and/or a beta-blocker. #p < 0.001 as compared with the enrollment left ventricular ejection fraction indicating significant improvement in left ventricular ejection fraction as compared with the left ventricular

18/20 completed therapy, no treatment>1 year for metastatic disease
Role of early detection of Trastuzumab cardiotoxicity

- Completion of chemotherapy is primary goal
- Cardioprotective regimen initiation possibly indicated with biomarker rise, changes in echo findings EF decline >10%, EF <50%
- Greater ejection fraction decline (EF <40%) or symptoms are stopping/modification points for chemotherapy if suitable alternative available
- Role of markers, LV Strain as stopping points undefined. Low threshold for “cardioprotection”
- FDA insert: Stop herceptin while EF <50%
  - Restart if EF improves to >50%
Surveillance & management
trastuzumab toxicity

➢ Package insert: Quarterly echoes recommended
  ❖ Limited yield for MBC patients on chronic Trastuzumab
    * Less frequent if stable normal EF no prior toxicities:

➢ Aggressive risk factor management to minimize CVD

➢ ACEI/Beta blocker for decline in EF >10% esp if below LLN
  ❖ Variability in EF problematic
  ❖ Markers, LV strain decline may be helpful
    * diastolic dysfunction not actionable
  ❖ Patients favor effective cancer therapy over total heart protection

➢ Interruption of therapy with EF >40% not mandatory
  ❖ Prolonged Herceptin for metastatic breast cancer feasible
### 2005: Two Cardiotoxic chemotherapeutic classes

**Anthracyclines and anti-HER2 agents**

<table>
<thead>
<tr>
<th>Characteristic agent</th>
<th>Type I (myocardial damage)</th>
<th>Type II (myocardial dysfunction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical course, response to CRCD therapy</td>
<td>May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress</td>
<td>High likelihood of recovery (to or near baseline cardiac status) in 2-4 months (reversible)</td>
</tr>
<tr>
<td>Dose effects</td>
<td>Cumulative, dose related</td>
<td>Not dose related</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Free radical formation, oxidative stress/damage</td>
<td>Blocked ErbB2 signaling</td>
</tr>
<tr>
<td>Ultrastructure</td>
<td>Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)</td>
<td>No apparent ultra structural abnormalities</td>
</tr>
<tr>
<td>Noninvasive cardiac testing</td>
<td>Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion</td>
<td>Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion</td>
</tr>
<tr>
<td>Effect of rechallenge</td>
<td>High probability of recurrent dysfunction that is progressive, may result in intractable heart failure and death</td>
<td>Increasing evidence for the relative safety of rechallenge; additional data needed</td>
</tr>
<tr>
<td>Effect of late sequential stress</td>
<td>High likelihood of sequential stress related cardiac dysfunction</td>
<td>Low likelihood of sequential stress-related cardiac dysfunction</td>
</tr>
</tbody>
</table>

Abbreviation: CRCD, chemotherapy-related cardiac dysfunction.

Ewer & Lippmann, JCO May 2005
Development of Anthracyclines

➢ Derived from Italian soil streptomycetes near Adriatic Sea
  ❖ Area was near home of ancient Dauna tribe
  ❖ Reddish (ruby) color
  ❖ Hence names adriamycin, daunarubicin

➢ Daunorubicin (Daunomycin) First anthracycline developed
  ✧ ALL, AML

➢ Adriamycin (Doxorubicin)
  ✧ Breast, sarcomas, lung, ovarian, lymphoma, Wilms, GI

➢ Epirubicin
  ✧ Breast, Gastric, Carcinoid, Ovarian, Esophageal, Soft Sarcoma

➢ Idarubicin (4-demethoxyDaunorubicin) : AML

➢ Valrubicin: Bladder
Daunomycin* introduced 1967 with concerns about cardiotoxicity

DAUNOMYCIN, AN ANTITUMOR ANTIBIOTIC, IN THE TREATMENT OF NEOPLASTIC DISEASE
Clinical Evaluation with Special Reference to Childhood Leukemia

Charlotte Tan, MD, Hideko Tasaka, MD, Kou-Ping Yu, MD, M. Lois Murphy, MD, and David A. Karnofsky, MD

Cancer 1967;20:333

Daunomycin is a new antibiotic in the anthracycline group obtained from Streptomyces peucetius. It consists of a pigmented aglycone (daunomycinone) in glycoside linkage with an amino sugar (daunosamine). Differences in the biological effects of daunomycin, which reacts with DNA, and actinomycin D which complexes with DNA in a different manner to inhibit RNA production, are discussed. The toxic effects of daunomycin are a severe local reaction if the drug extravasates, bone marrow depression resulting in leucopenia, anemia, thrombocytopenia and bleeding, fever, oral ulcers and alopecia. In patients receiving maintenance doses of daunomycin the development of tachypnea, tachycardia pulmonary insufficiency, heart failure and hypotension possibly is associated with daunomycin but the evidence is unclear. Sixty per cent of children with leukemia obtained brief complete or partial hematological remissions from a single course of daunomycin. The remission could be prolonged by maintenance therapy. Daunomycin is temporarily effective in some cases of neuroblastoma, reticulum cell sarcoma and rhabdomyosarcoma.

1967: 60% tumor response was major breakthrough in ALL
Cardiotoxicity: “The Evidence is Unclear”

*Daunorubicin=Adriamycin
1973: 1\textsuperscript{st} focused report on anthracycline cardiotoxicity
Pathology accurate, Safe dose overestimated

- 399 treated patients, 11 acute HF, 8 deaths all within 3 weeks of onset of HF

- **Dose Dependent:** 0.27\% HF $<550\text{mg}/\text{M}^2\text{BSA}$, 30\% $>550$

- **EKG:** Loss of voltage, **CXR:** Pulmonary edema, *No Echoes*, Microscopy: Cardiomyocyte vacuolization

- **Safe dose** $<500\text{mg}/\text{m}^2\text{BSA}$
2019: Dose Dependent HF risk
150, 250, 350 mg/M² BSA thresholds

There is no safe therapeutic dose of Adriamycin
Liposomal or pegylated liposomal doxorubicin somewhat less toxic
Varying infusion rate or dose frequency used to mitigate toxicity

Figures: Saro Armenian
1979: Advancing age at treatment increases HF risk

VonHoff et al Annals Int Med 1979; 91: 710
2015: Younger age at treatment: *Longer latency, similar CVD risk curves*

Hodgkin's Survivors: Anthracycline & Radiation

**A** Cumulative incidence of any cardiovascular disease

JAMA Int Med 2015; 175:1007
Radiation dose amplifies anthracycline risk
Dexrazoxane: Specific inhibition of anthracycline effect on Topoisomerase 2B

- Anthracyclines inhibit Topoisomerase 2A in cancer cells & inhibit Topoisomerase 2Beta in cardiomyocytes causing DNA breaks, ROS generation and mitochondria inhibition
- Dexrazoxane inhibits Top2B to protect myocardial cells with no effect on Top2A in cancer cells

![Mechanism of Doxorubicin-Induced Cardiotoxicity](image.png)

Doxorubicin inhibits Topoisomerase 2β to induce DNA double-strand break, leading to p53 activation and death of cardiomyocytes. Doxorubicin-bound Topoisomerase 2β binds to promoters of antioxidative genes and PGC-1 that are required for expression of antioxidative enzymes and electron transport chains. Thus, Topoisomerase 2β is able to account for the 3 hallmarks of doxorubicin-induced cardiotoxicity: cardiomyocyte death, generation of reactive oxygen species (ROS), and mitochondriopathy (24,25).
Dexrazoxane prevents anthracycline cardiotoxicity in childhood ALL

Cardioprotectants: *Dexrazoxane*

The Effect of Dexrazoxane on Myocardial Injury in Doxorubicin-Treated Children with Acute Lymphoblastic Leukemia


Citation: van Dalen EC, Caron HN, Dickinson HO, Kremer LCM. Anthracyclines. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art.

Figure 1. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane / placebo, outcome: 1.1% heart failure.
Dexrazoxane FDA approved for metastatic breast cancer with advancing dose of adriamycin >300 mg/m²

ZINECARD is indicated for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy.
KU Cardiooncolgy Case Study: 38 year old woman with Hodgkin Lymphoma whose cure depends on adriamycin and EF 40%

- 38 year old with new Dx Hodgkin’s Lymphoma
  - Generally healthy mother of 2, Working full time financial analyst
- Painless 2 cm supraclavicular node, no fevers or weight loss: Bx Hodgkin Lymphoma
- CT Chest: Mediastinal nodes extending to encase left vertebral, left subclavian and left common carotid arteries, numerous satellite nodes. No myocarditis on staging PET
- Echo & MUGA EF 40%-45%
- No guidance in oncology for adriamycin w/ baseline EF <50%
Initial Patient Course

➢ Cardio-oncology Rec
  ❖ Assessment: Low CV risk patient, High need for adriamycin
  ❖ Recommend
    ✶ Consent for high risk adriamycin w/ no safety data on treatment
    ✶ Carvedilol 3.125 & lisinopril 2.5 2 days pre-ABVD
    ✶ Start optimal ABVD protocol: adriamycin 25 mg/m², bleomycin, dacarbazine, & Vinblastine q 2 weeks for 12 treatments

➢ BNP & Troponins with every treatment
➢ Echos q 1 to 2 treatments
➢ Cardio-oncology clinic visits, drug titration
Hypotension w/ sx, Carvedilol held at 12.5 BID, Lisinopril 2.5

BNP <50, Trop 0.1-0.2 for 3 months

LVEF visually improved, estimate 55% p 6 weeks

FDG-PET: “Mixed response” Abdominal activity noted, reclassified at Stage III.

After 150 mg/m2 adriamycin: BNP uptick ~250, trop 0.04-0.05
EF decline 45% carvedilol 12.5 BID.

- Lisinopril had been held d/t creat rise w/ amphotericin for pulm histo (EBUS/BAL)

Cardio-oncology rec: Continue Adriamycin 25mg/M2 q 2 weeks, Carvedilol 12.5 BID
Clinical course ii

- EF after adria 250mg/M2: LV function visibly improved estimated normal EF 55%.
- 1 month post ABVD, Dyspnea, DLCO decline, Markers, EF 55%. Stable
  - Dx Bleo toxicity
- 6 months post ABVD
  - Lymphoma in remission
  - EF 45%, non-adherent to carvedilol, candesartan>>Med adherence, regular exercise emphasized
- 6 months later: CMR EF 52%, normal LV mass & volume, No LGE
  - Continuing Carvedilol 12.5 BID, candesartan 4.
Case series in 2019: Upfront Dexrazoxane + doxorubicin: “Dex-Dox” with baseline LV dysfunction

All patients stable on max tolerated GDMT
Stage B or C heart failure

Prior to Dexrazoxane protocol:
3 patients, 76 years,
EF 42.5%

Dexrazoxane protocol before each dose anthracycline:
5 patients, 70.6 years
EF 39%, 1 w/ ICD baseline
Case series in 2019: Upfront Dexrazoxane + doxorubicin: “Dex-Dox” with baseline LV dysfunction

Outcomes without Dexrazoxane:
EF 18% p treatment (Baseline 42%)
All 3 admitted with ADHF, 2 died

Outcomes with Dexrazoxane:
All completed planned chemo 280-300mg/m²
No decompensated HF or marker abnormality
EF 34% post treatment (Baseline 39%)
All alive 12-30 months: 4 complete 1 partial remission
Adriamycin with pre-treatment LV dysfunction

- Assess likelihood of manageable causes: CAD, Takutsubo, Myocarditis
- If low risk patient EF >40%, no RFs, Adriamycin may be well tolerated
- Acute adriamycin toxicity not inevitable with baseline EF <50%, favorable risk factor profile
- Intra-therapy surveillance protocols not defined
- Upfront Dexrazoxane promising, off label option
Monitoring for anthracycline toxicity

<table>
<thead>
<tr>
<th>Method</th>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endomyocardial biopsy</td>
<td>Provides histological evidence of cardiotoxicity</td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires specialist input for performing the procedure and interpreting the findings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small sample of myocardium tested</td>
</tr>
<tr>
<td>Radionuclide ventriculography</td>
<td>Well-established and well-validated method to determine ejection fraction</td>
<td>Invasive—exposes patients to radiation which limits its repeatability</td>
</tr>
<tr>
<td>(multiple uptake gated acquisition</td>
<td></td>
<td>Low spatial resolution</td>
</tr>
<tr>
<td>scan)</td>
<td>Can also assess regional wall motion and diastolic function</td>
<td>No information on valve function</td>
</tr>
<tr>
<td></td>
<td>(nonstandard)</td>
<td>LVEF measurements are not sensitive for the early detection of preclinical cardiac disease</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Provides a wide spectrum of information on cardiac morphology and function</td>
<td>Image quality limits use in some patients</td>
</tr>
<tr>
<td></td>
<td>Does not expose patients to ionising radiation</td>
<td>LVEF measurements time consuming and operator dependent with limited reproducibility</td>
</tr>
<tr>
<td></td>
<td>Tissue Doppler imaging may improve detection of systolic and diastolic</td>
<td>LVEF measurements are not sensitive for the early detection of preclinical cardiac disease</td>
</tr>
<tr>
<td></td>
<td>dysfunction</td>
<td>Both FS and LVEF are affected by preload and afterload</td>
</tr>
<tr>
<td>Stress echocardiography</td>
<td>Cardiac abnormalities that remain occult at rest can be detected</td>
<td>Not routinely carried out</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mixed reports on ability to enhance diagnostic sensitivity</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Troponin is a highly specific and sensitive</td>
<td>Data regarding clinical value are limited</td>
</tr>
<tr>
<td></td>
<td>biomarker for detection of myocardial damage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Potentially useful screening tool</td>
<td></td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>Valuable tool to assess myocardial function and damage</td>
<td>High costs of repeated examinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited availability</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>Image quality similar to magnetic resonance imaging</td>
<td>High radiation dose</td>
</tr>
<tr>
<td></td>
<td>Low temporal resolution</td>
<td>Limited availability</td>
</tr>
<tr>
<td>Scintigraphy</td>
<td>Sensitive method to detect myocyte damage in patients after doxorubicin</td>
<td>Larger prospective trials required to ascertain potential role</td>
</tr>
<tr>
<td></td>
<td>therapy</td>
<td></td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; FS, fractional shortening.

Baseline Echo is standard of care
No established or proposed protocols for monitoring LV function during treatment
Summary: Preventing & treating Adriamycin Cardiotoxicity

➢ First Objective: Treat Curable Cancer with full front line chemotherapy

➢ No clinically relevant cardioprotection from ACEI/ARB or Beta Blocker with normal EF

➢ Baseline EF reduction usually deters use of adria
  - Dexrazoxane up-front promising but off label
  - Mild Declines in EF should not stop curative intent therapy
    * Consider HFrEF medication
  - New abnormalities in Diastolic function or Strain should not stop cancer treatment, no evidence that interventions have merit but cardio-protection possibly beneficial
Immune Checkpoint Inhibitors: 
High profile targeted Cancer therapy 
High impact cardiotoxicity
Immune Checkpoint Inhibitors in the spotlight

December, 2015: Pembrolizumab pardons a president with metastatic melanoma

Understanding Jimmy Carter's Surprise Cancer Turnaround: A Conversation with Jedd Wolchok

By Matthew Tontonoz, Wednesday, December 9, 2015

Former President Jimmy Carter announced this week that he is "cancer free" after receiving treatment for advanced melanoma. (Photo Credit: The Carter Center.)

Summary

- Jimmy Carter announced this week he is free of melanoma. In addition to surgery and radiation, Mr. Carter was treated with a new immunotherapy drug called pembrolizumab.
- Combining immunotherapies with other treatments may improve outcomes for some patients.

Highlights

- Melanoma is a type of skin cancer that can spread to other organs, including the brain.
- Immunotherapy drugs like the one Mr. Carter received are offering new hope to patients with metastatic melanoma.
- Combination treatments may improve outcomes for some patients.

DTC advertising: Longer life spans with nivolumab for relapsed non-small Cell lung cancer

May 2019: President Carter fractures hip while Turkey hunting, Home after surgery

2018 Nobel Prize in Medicine awarded to 2 developers of immunotherapy as cancer treatment
**Immune Checkpoint Inhibitors**

2011: 1st FDA approved ICI - Ipilimumab in Melanoma

2018: Multiple drugs & indications

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**U.S. FDA Approved Immune-Checkpoint Inhibitors**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Drugs and Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous Cell Head &amp; Neck Cancer</td>
<td>1L nivolumab after platinum chemotherapy, 1L pembrolizumab after platinum chemotherapy</td>
</tr>
<tr>
<td>Malignant Melanoma</td>
<td>Adj. / 1L ipilimumab, 1L nivolumab ± ipilimumab, Adj. nivolumab, 1L pembrolizumab, Merkel Cell Carcinoma, 2L avelumab</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>2L nivolumab after sorafenib</td>
</tr>
<tr>
<td>Adv. Renal Cell Carcinoma</td>
<td>2L nivolumab after anti-angiogenic therapy</td>
</tr>
<tr>
<td>Locally Adv. or Met. Urothelial Cancer</td>
<td>1L nivolumab after platinum chemotherapy, 1L pembrolizumab after platinum chemotherapy, or in platinum-ineligible patients</td>
</tr>
<tr>
<td>Non-Small Cell Lung Cancer</td>
<td>1L pembrolizumab TPS=50%, 1L pembrolizumab + pemetrexed/carboplatin in non-squamous NSCLC</td>
</tr>
<tr>
<td>Malignant Melanoma</td>
<td>2L pembrolizumab TPS=1%, 2L nivolumab, 2L atezolizumab NSCLC, Maintenance avelumab after chemoradiation</td>
</tr>
<tr>
<td>Gastric &amp; GEJ Carcinoma</td>
<td>3L pembrolizumab after fluoropyrimidine- and platinum-CTX +/- HER2 therapy &amp; CPS=1</td>
</tr>
<tr>
<td>Classical Hodgkin Lymphoma</td>
<td>4L pembrolizumab, 3L nivolumab after auto-HSCT and BV, 4L nivolumab and after auto-HSCT</td>
</tr>
<tr>
<td>MSI-H or dMMR Cancers</td>
<td>2L nivolumab in CRC after FOLFOXIRI, 2L pembrolizumab in CRC after FOLFOXIRI, 2L pembrolizumab in any MSI-H/dMMR cancer</td>
</tr>
</tbody>
</table>

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March 8, 2019 FDA approves atezolizumab for triple Neg Stage II or IV Breast Ca

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*Figure: medi-paper.com*
Checkpoint Inhibition: Tumor produces “Fake ID” to escape T Cell attack

Checkpiont Inhibitors reveal tumor cells at checkpoints, facilitate immunity at 3 sites: CTLA-4, PD-1 & PD-L1.

Tumor antigens block Foreign MHC interactions with T Cell receptors

Tumor antigens block CTLA-4 activation of T Cells

Tumor PD-L1 blunts PD-1 triggered T cell cytotoxicity

CTLA-4 inhibition

PD-1 inhibition

PD-L1 inhibition

Tocchetti et al JACC March 2018;71:17
Immune Checkpoint Inhibition (ICI): Multifaceted facilitation of natural immune response to tumors

Dual Checkpoint Inhibition
- More effective
- More Toxicity
- Common combination
  - CTLA-4
  - PD-1

Figure Moslehi, ACC CardioOncology 2018
Autoimmune reaction against many tissues
Myocarditis mechanism?: Activated T Cells attack Cardiomyocytes with PD-L1, shared tumor antigens

Tocchetti et al JACC March 2018;71:1765
Fatal Myocarditis
Dual Checkpoint inhibition therapy
Ipilimumab & Nivolumab

Initial report of two fatal cases NEJM Nov 2016

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

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Margaret L. Compton, M.D., Spyridon Chalakis, M.D., Joshua Gorham, B.A.,
Yaomin Xu, Ph.D., Melissa Hicks, Ph.D., Igor Puzanov, M.D.,
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Mark A. Pilkington, M.D., Ph.D., Laura Craig-Owens, M.D., Nina Kola, M.D.,
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Janis M. Taube, M.D., Luis A. Diaz, Jr., M.D., Robert A. Anders, M.D.,
Jeffrey A. Sosman, M.D., and Javid J. Moslehi, M.D.

SUMMARY

Immune checkpoint inhibitors have improved clinical outcomes associated with numerous cancers, but high-grade, immune-related adverse events can occur, particularly with combination immunotherapy. We report the cases of two patients with melanoma in whom fatal myocarditis developed after treatment with ipilimumab and nivolumab. In both patients, there was development of myocarditis with rhabdomyolysis, early progressive and refractory cardiac electrical instability, and myocarditis with a robust presence of T-cell and macrophage infiltrates. Selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumors and skeletal muscle. Pharmacovigilance studies show that myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab, which suggests that our patients were having a rare, potentially fatal, T-cell-driven drug reaction. (Funded by Vanderbilt-Ingram Cancer Center Ambassadors and others.)

Normal LVSF, Refractory arrhythmias, death
Sine Wave Ventricular Tachycardia
not torsades des pointes

Electrocardiographic (EKG) Disturbances with Immune-Checkpoint Inhibitor Associated Myocarditis

Courtesy of Olenchock, BWH. Ahmad, Yale
8 Center registry findings: ICI myocarditis

- **35 patients**
  - 1.14% incidence at MGH
- **29% Female**
- **54% Myocarditis sole SE**
- **Risk Factors**
  - 34% Dual ICI therapy
  - 66% Single agent ICI
  - DM in 34% RR 3.36
- **46% w/ MACE** (Major Adverse CV events)
  - CV death, cardiac arrest, cardiogenic shock, and hemodynamically significant complete heart block

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Myocarditis in Patients Treated With Immune Checkpoint Inhibitors


**ABSTRACT**

**BACKGROUND** Myocarditis is an uncommon, but potentially fatal, toxicity of immune checkpoint inhibitors (ICI). Myocarditis after ICI has not been well characterized.

**OBJECTIVES** The authors sought to understand the presentation and clinical course of ICI-associated myocarditis.

**METHODS** After observation of sporadic ICI-associated myocarditis cases, the authors created a multicenter registry with 8 sites. From November 2013 to July 2017, there were 35 patients with ICI-associated myocarditis, who were compared to a random sample of 105 ICI-treated patients without myocarditis. Cowarates of interest were extracted from medical records including the occurrence of major adverse cardiac events (MACE), defined as the composite of cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block.

**RESULTS** The prevalence of myocarditis was 1.14% with a median time of onset of 34 days after starting ICI (interquartile range 21 to 75). Cases were 65 ± 13 years of age, 25% were female, and 54% had no other immune-related side effects. Relative to controls, combination ICI (34% vs. 2%; p < 0.001) and diabetes (34% vs. 13%; p = 0.01) were more common in cases. Over 102 days (interquartile range 62 to 214) of median follow-up, 16 (46%) developed MACE; 38% of MACE occurred with normal ejection fraction. There was a 4-fold increased risk of MACE with troponin T of ≥1.5 ng/ml (hazard ratio 4.0; 95% confidence interval 1.5 to 10.9; p = 0.003). Steroids were administered in 89%, and lower steroids doses were associated with higher residual troponin and higher MACE rates.

**CONCLUSIONS** Myocarditis after ICI therapy may be more common than appreciated, occurs early after starting treatment, has a malignant course, and responds to higher steroid doses. (J Am Coll Cardiol 2018;■:■:■)

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Mahmood et al JACC Pub Online March 2018
Troponin elevation, abnormal EKG, abnormal BNP more common than EF <50%

- Mean Onset 34 Days after start of therapy
- + Troponin >90%
- ~50% with EF <50%
- 38% w/ MACE had EF >50%
- ~90% treated with steroids
  - Higher troponins and higher MACE rates with lower steroid doses

Mahmood et al JACC Pub Online March 2018
Cardiac Symptoms in patient on Immune Checkpoint Inhibitor therapy? Consider Myocarditis

**CENTRAL ILLUSTRATION** Algorithm for Work-Up and Management of Immune-Mediated Myocarditis

- Patient on immune checkpoint inhibitors (ICI) or prior ICI use
  - Patient presenting with new cardiovascular (CVD) symptoms
    - Electrocardiogram (EKG) and troponin test
      - Normal results
        - New ventricular arrhythmia or conduction system disease?
          - Y: Possible myocarditis: Admit patient
            - Stop ICI therapy; Urgent Cardiology/Cardio-Oncology consult; Determine whether patient is stable or unstable to dictate treatment
          - N: Outpatient echo. and NT-proBNP testing
      - Elevated results
        - Elevated troponin/abnormal EKG
        - If indeterminate troponin, retest to eliminate false result

Algorithm based on study findings, and institutional experience with 35 cases of ICI-associated myocarditis. CVD = cardiovascular; EKG = electrocardiogram; ICI = immune checkpoint inhibitors.
ICI: LVSD with Shock or VT without LVSD: Empiric management

Immune-Checkpoint Inhibitor Cardiovascular Toxicity in 2018

• Screening
  – ECG, troponin in high-risk individuals (combination therapy)
• Diagnosis
  – Combination of biomarkers, imaging and biopsy
  – Much consider biopsy
• Treatment
  – High dose steroids
  – Antithymoglobulin (ATG)
  – Other therapies directed at T cells? Tacrolimus, MMF

Figure Moslehi, ACC CardioOncology 2018
KU Cardiooncology Experience
Complete Heart block & syncope in heart transplant patient on CKI for Melanoma and RCC

- 77 year old man s/p 1999 cardiac transplant
- 1999 Cyclosporine, Mycophenolate, Prednisone
- 2003 Moderate rejection Prednisone boost to 5/day
- 2009: Reduce Myco, cyclo d/t recurrent skin cancers
- 11/2018 Dyspnea: CT survey: Lung mets, renal mass
- 1/10/19 Begin Nivolumab for Bx proven metastatic melanoma and Renal Cell Cancer.
- 4/1/19 Syncope, complete heart block, Severe cardiac rejection, EF 30%, Permanent pacer, Augment immunosuppression. Stop Nivolumab
  - 4/22/19: CT survey: regression of pulmonary mets, RCC stable
  - 4/24/19 Rejection resolved on Biopsy, EF 45%
- Oncology: Melanoma will grow without nivolumab
Collaborative Cardiooncology, oncology and patient/family plan

- No precedents for reintroduction of CKI after near fatal cardiotoxicity (Gr 4)
- Augmentation of cardiac immunosuppression might protect heart but not blunt anti-tumor effect.
- Suspension of CKI therapy will unleash tumors
- Reintroduction Nivolumab with serial echoes and biopsies reasonable, but possibly more rapidly fatal than waiting for tumor to grow.
Clinical follow-up

➢ 5/6/19 Nivolumab resumed
➢ 7/24/19 CT Survey: Lung and Renal masses stable
➢ 4 biopsies 5/22-9/11 Gr0 to GrI rejection
➢ Echo 8/28/19: Hyperdynamic LV function EF >70%, RV normal size and function

❖ Lessons Learned
  ❖ Cardiac immunosuppression allowed resumption of Nivolumab without recurrent rejection over 5 months
  ❖ No early loss of anti-tumor effect of Nivolumab with rigorous triple agent cardiac immunosuppression.
Questions/Comments?

Don’t Forget: On Monday 10/26 send 3 facts/ideas you recall from this presentation to cbporter@kumc.edu