Cardiotoxicity: The View of the Cardiologist

Dr. Yael Peled
The Leviev Heart Center
Sheba Medical Center, Tel Hashomer
Cardio-Oncology Interactions:

1. Cardiotoxicity following chemotherapy
2. Coexistence of cancer and CVD
   Aging & common risk factors

*cardiac disease and cancer together make up more than 70% of disease-related mortality in the developed world*

Sanz et al. JACC 2007
in elderly breast cancer prevalence of HF is increased substantially compared with the general population

Lindenfeld, Prog Cardiovasc Dis 2010

in breast cancer patients who did not receive chemotherapy, the risk of HF at 5 and 10 years was still twofold and fivefold greater than in the general population.
CVD affects survival and QOL independent of a coexisting cancer. Indeed, the prognosis of HF may be more limiting than some cancers. Accordingly, the onset of HF may change the therapeutic priorities of caregivers and patients.
Cardiotoxicity of Anticancer Treatments

- Cardiomyopathy
- Vascular injury
  - Ischemia (5-FU, capecitabine, bevacizumab)
  - Hypertension (sunitinib, sorafenib, bevacizumab)
- Pericardium- imbalance in fluid equilibrium, pericardial thickening
- Arrhythmias (Arsenic trioxide, paclitaxel, thalidomide)
- Venous Thromboembolic Disease (cisplatin, thalidomide, erlotinib)
- Cardiovascular toxicity induced by radiotherapy
<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>

**Type I (permanent damage) anticancer agents**
- Doxorubicin (anthracycline)
- Daunorubicin (anthracycline)
- Epirubicin (anthracycline)
- Idarubicin (anthracycline)
- Mitoxantrone (anthracenedione)
- Cyclophosphamide (oxazophorine alkylating agent)

**Type II (reversible damage) anticancer agents**
- Trastuzumab (monoclonal antibody)
- Sunitinib (tyrosine kinase inhibitor)
- Lapatinib (tyrosine kinase inhibitor)
Topics to be discussed

• Trastuzumab-Related Cardiac Dysfunction

• Anthracyclines-Related Cardiac Dysfunction

• General Approach: Cardio-Oncology Collaboration
Trastuzumab (Herceptin) - Related Cardiac Dysfunction
Trastuzumab - Mechanism of Action

Extracellular effects of trastuzumab:
- Inhibition of cleavage of HER2 extracellular domain
- Interference with homodimer and heterodimer formation between HER-family receptors
- Antibody-dependent immune mechanisms

Intracellular effects of trastuzumab:
- Induction of apoptosis
- Decreased cell proliferation
- HER2 downregulation, dephosphorylation, or both
- Decreased VEGF production
- Potentiation of chemotherapy
- Modulation of downstream signal paths
- Altered cross-talk with other signal paths

Amplified number of HER2 genes on chromosome 17
# Efficacy in Metastatic Breast Cancer (MBC)

**Table 2. Results of an Intention-to-Treat Analysis of the End Points.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Chemotherapy plus Trastuzumab (N=235)</th>
<th>Either Type of Chemotherapy Alone (N=234)</th>
<th>An Anthracycline, Cyclophosphamide, and Trastuzumab (N=143)</th>
<th>An Anthracycline and Cyclophosphamide Alone (N=138)</th>
<th>Paclitaxel and Trastuzumab (N=92)</th>
<th>Paclitaxel Alone (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to disease progression — mo</td>
<td>7.4</td>
<td>4.6</td>
<td>7.8</td>
<td>6.1</td>
<td>6.9</td>
<td>3.0</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk of progression (95% CI)</td>
<td>0.51 (0.41–0.63)</td>
<td></td>
<td>0.62 (0.47–0.81)</td>
<td>0.38 (0.27–0.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to treatment failure — mo</td>
<td>6.9</td>
<td>4.5</td>
<td>7.2</td>
<td>5.6</td>
<td>5.8</td>
<td>2.9</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk of treatment failure (95% CI)</td>
<td>0.58 (0.47–0.70)</td>
<td></td>
<td>0.67 (0.52–0.86)</td>
<td>0.46 (0.33–0.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median survival — mo</td>
<td>25.1</td>
<td>20.3</td>
<td>26.8</td>
<td>21.4</td>
<td>22.1</td>
<td>18.4</td>
</tr>
<tr>
<td>P value</td>
<td>0.046</td>
<td></td>
<td>0.16</td>
<td>0.17</td>
<td>0.80 (0.56–1.11)</td>
<td></td>
</tr>
<tr>
<td>Relative risk of death (95% CI)</td>
<td>0.80 (0.64–1.00)</td>
<td></td>
<td>0.82 (0.61–1.09)</td>
<td>0.80 (0.56–1.11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*N Engl J Med, Vol. 344, No. 11 · March 15, 2001*
### Table 4. Adverse Events That Occurred in More Than 10 Percent of Patients as a Group.

<table>
<thead>
<tr>
<th>Type or Location of Adverse Event</th>
<th>Chemotherapy Plus Trastuzumab (N=234)</th>
<th>Chemotherapy Alone (N=230)</th>
<th>An Anthracycline and Cyclophosphamide and Trastuzumab (N=143)</th>
<th>An Anthracycline and Cyclophosphamide Alone (N=135)</th>
<th>Paclitaxel and Trastuzumab (N=91)</th>
<th>Paclitaxel Alone (N=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>27 (3)</td>
<td>20 (3)</td>
<td>23 (2)</td>
<td>18 (2)</td>
<td>34 (3)</td>
<td>22 (4)</td>
</tr>
<tr>
<td>Atelectra</td>
<td>57 (7)</td>
<td>56 (7)</td>
<td>54 (7)</td>
<td>55 (7)</td>
<td>62 (8)</td>
<td>57 (8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>31 (4)</td>
<td>22 (4)</td>
<td>27 (2)</td>
<td>16 (2)</td>
<td>56 (8)</td>
<td>30 (5)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>24 (3)</td>
<td>24 (3)</td>
<td>20 (3)</td>
<td>21 (2)</td>
<td>30 (3)</td>
<td>27 (5)</td>
</tr>
<tr>
<td>Chills</td>
<td>58 (&lt;1)</td>
<td>8 (&lt;1)</td>
<td>55 (&lt;1)</td>
<td>11 (2)</td>
<td>42 (1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Fever</td>
<td>53 (8)</td>
<td>29 (4)</td>
<td>50 (11)</td>
<td>83 (7)</td>
<td>47 (2)</td>
<td>23 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>41 (4)</td>
<td>30 (4)</td>
<td>44 (3)</td>
<td>31 (5)</td>
<td>36 (7)</td>
<td>28 (2)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>22 (10)</td>
<td>5 (2)</td>
<td>27 (16)</td>
<td>8 (3)</td>
<td>13 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Digestive tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>28 (&lt;1)</td>
<td>22 (2)</td>
<td>31 (0)</td>
<td>26 (2)</td>
<td>24 (1)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>32 (1)</td>
<td>28 (3)</td>
<td>36 (2)</td>
<td>28 (3)</td>
<td>25 (0)</td>
<td>37 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45 (1)</td>
<td>27 (3)</td>
<td>45 (1)</td>
<td>25 (3)</td>
<td>45 (1)</td>
<td>30 (5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>66 (5)</td>
<td>66 (7)</td>
<td>76 (6)</td>
<td>79 (10)</td>
<td>50 (3)</td>
<td>48 (3)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>22 (&lt;1)</td>
<td>21 (0)</td>
<td>30 (1)</td>
<td>31 (3)</td>
<td>10 (0)</td>
<td>7 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47 (5)</td>
<td>40 (7)</td>
<td>58 (3)</td>
<td>49 (8)</td>
<td>87 (9)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Hematologic and lymphatic systems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>27 (2)</td>
<td>19 (2)</td>
<td>35 (3)</td>
<td>25 (2)</td>
<td>14 (1)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>41 (11)</td>
<td>26 (9)</td>
<td>52 (15)</td>
<td>33 (14)</td>
<td>24 (6)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>20 (4)</td>
<td>14 (2)</td>
<td>8 (&lt;1)</td>
<td>10 (&lt;1)</td>
<td>21 (4)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>23 (3)</td>
<td>22 (3)</td>
<td>13 (&lt;1)</td>
<td>13 (&lt;1)</td>
<td>38 (7)</td>
<td>36 (6)</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>29 (&lt;1)</td>
<td>23 (&lt;1)</td>
<td>17 (0)</td>
<td>11 (0)</td>
<td>47 (2)</td>
<td>39 (1)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased coughing</td>
<td>43 (&lt;1)</td>
<td>26 (&lt;1)</td>
<td>43 (&lt;1)</td>
<td>28 (0)</td>
<td>42 (0)</td>
<td>22 (1)</td>
</tr>
<tr>
<td>Dyspnea not related to heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>30 (&lt;1)</td>
<td>16 (&lt;1)</td>
<td>30 (0)</td>
<td>18 (0)</td>
<td>22 (0)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>57 (26)</td>
<td>58 (35)</td>
<td>58 (25)</td>
<td>50 (42)</td>
<td>56 (26)</td>
<td>56 (26)</td>
</tr>
<tr>
<td>Rash</td>
<td>31 (&lt;1)</td>
<td>17 (&lt;1)</td>
<td>27 (0)</td>
<td>17 (&lt;1)</td>
<td>58 (1)</td>
<td>18 (1)</td>
</tr>
</tbody>
</table>

*The analysis of adverse events excluded five patients who were never treated.

A multivariate analysis showed that in this cohort of patients, a low baseline LVEF was significantly associated with cardiac events (HR, 0.9444; P = .001).

# Efficacy and Safety of Trastuzumab in the Adjuvant Setting

<table>
<thead>
<tr>
<th>Trial (number of patients)</th>
<th>Treatment arms</th>
<th>Definition of severe cardiotoxicity</th>
<th>Monitoring frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31 (n = 2030)</td>
<td>AC x4, Pacli x4, then observation AC x4, followed by Pacli x4 with concurrent tras x1y</td>
<td>Grade III/IV HF or cardiac death; or LVEF decrease &gt;15 points**</td>
<td>MUGA 3 weeks, 6 months, and 9 months after end of initial AC; and 2 months after last trastuzumab</td>
</tr>
<tr>
<td>NCCTG N9831 (n = 3505)</td>
<td>AC x4, Pacli x12w, then observation AC x4, Pacli x12w with concurrent tras x1y AC x4, Pacli x12w, followed by tras x1y</td>
<td>Grade III/IV HF or cardiac death; or LVEF decrease &gt;15 points**</td>
<td>MUGA or Echo at entry, after AC, and 8, 9, 16, and 21 months after entry</td>
</tr>
<tr>
<td>HERA (n = 5090)</td>
<td>Any CT regimen, then observation Any CT regimen, then tras x1y Any CT regimen, then tras x2y</td>
<td>Severe HF: symptomatic HF; or LVEF decrease &gt;10 points**</td>
<td>LVEF (Echo or MUGA) at baseline, 3, 6, 12, 18, 24, 30, 36, 60 months</td>
</tr>
<tr>
<td>BCIRG-006 (n = 3222)</td>
<td>AC x4, Doce x4, then observation AC x4, followed by Doce x4 with concurrent tras x1y DoceCarbo x6 with concurrent tras x1y</td>
<td>Grade III/IV HF; cardiac death; grade 3-4 arrhythmias; grade 3-4 ischemia/infarction; or LVEF decrease &gt;10 points*</td>
<td>After AC, after second dose of doctaxel, at end of CT, and 3, 12, and 36 months after randomization</td>
</tr>
<tr>
<td>FinHer (n = 232)*</td>
<td>DoceVmb x3, then CEF x3 DoceVmb x3 + Tras x9w, then CEF x3</td>
<td>Myocardial infarction; HF; or LVEF decrease &gt;15 points</td>
<td>Echo or MUGA before CT, after CEF, and 12 and 36 months after CT</td>
</tr>
</tbody>
</table>
Overall in The Adjuvant Treatment:

- **Severe HF (NYHA III/IV):**
  - Trastuzumab-treated pts up to 3.9%
  - Not trastuzumab tx pts up to 1.3%

- **Decline in EF of 10-15% or greater* ‡**
  - Trastuzumab-treated pts 3-34%
  - Not trastuzumab tx pts 2-17%

- *This excludes the FinHER trial, in which a decline in ejection fraction occurred more frequently in patients not receiving trastuzumab
- ‡ was mostly reversible
Risk Factors for Cardiotoxicity

- Previous or concurrent anthracycline use
- Age greater than 50 years
- Preexisting cardiac dysfunction
- High body mass index

**Does not increase the risk:**
- Adjuvant radiation therapy
- Diabetes
- Valvular heart disease
- Coronary artery disease
Proposed Mechanism of Cardiac Dysfunction

Murine experiments have shown that the ERB2 receptor plays a crucial role in cardiogenesis and when not present in the heart, the resulting lack of signaling leads to either in-utero death or early severe dilated cardiomyopathy.

O’zcelik et al. PNAS, 2002

Trastuzumab, by inhibiting the ErbB2 receptor, leads to a loss of the neuregulin-dependent pathways that result in the survival of cardiac myocytes.

Chien et al. NEJM, 2006
The evaluation of left ventricular function for patients being considered for, or receiving Trastuzumab (Herceptin) therapy

KF Fox

1. The NICE have recently extended their guidance on indications for Trastuzumab. As part of the care of patients considered for Trastuzumab pre-treatment measurement of LV function is required and 3 monthly during treatment according to most protocols. This is because of the known potential for cardiac damage occurring in patients receiving Trastuzumab.

2. Although local guidelines may vary, current guidelines typically state that patients should not normally be commenced on Trastuzumab if their baseline Ejection Fraction (EF) is ≤55%. If the EF falls by more than 10% or to <50% cessation of treatment should be considered.
Heart Failure Treatment

• Trastuzumab-related cardiotoxicity usually responds to standard medical treatment for heart failure and discontinuation of trastuzumab in most, although not all, patients.

Reversibility & Rechallenge

• Trastuzumab-related cardiotoxicity is largely reversible in the majority of cases, and treatment continuation and/or resumption of trastuzumab after resolution of cardiac abnormalities may be safe in some women.
### Practical Approach

#### Table 3

<table>
<thead>
<tr>
<th>Treatment phase</th>
<th>Patient profile</th>
<th>Management strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before trastuzumab-based therapy</td>
<td>A. No cardiac history or risk factors with normal LVEF</td>
<td>Treat and monitor LVEF every 3 months</td>
</tr>
<tr>
<td></td>
<td>B. Cardiac history and/or risk factors with normal LVEF</td>
<td>Treat. Ask about symptoms and perform thorough PE before each cycle Measure troponin level after therapy and BNP level before next cycle</td>
</tr>
<tr>
<td></td>
<td>C. Decreased LVEF</td>
<td>Trastuzumab holiday for 1 mo A. Treat HF and remeasure 1. Return to baseline. Restart trastuzumab 2. Remains low: intensify HF treatment and remeasure 3. If LVEF remains low: individual decisions</td>
</tr>
<tr>
<td>During trastuzumab-based therapy</td>
<td>First decrease in LVEF</td>
<td>A. Stop trastuzumab B If trastuzumab only option: “Holiday” and maximize HF Rx</td>
</tr>
<tr>
<td></td>
<td>Second decrease in LVEF</td>
<td>No monitoring post treatment completion</td>
</tr>
<tr>
<td>Completion of</td>
<td>No change in LVEF and no symptoms during treatment</td>
<td>Continue HF treatment</td>
</tr>
<tr>
<td>trastuzumab-based therapy</td>
<td>LVEF decreased or symptoms</td>
<td>Monitor according to clinical practice for HF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

_J.R. Carver / Progress in Cardiovascular Diseases 53 (2010) 130–139_
Before Trastuzumab-Based Therapy

<table>
<thead>
<tr>
<th>Treatment phase</th>
<th>Patient profile</th>
<th>Management strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before trastuzumab-based therapy</td>
<td>A. No cardiac history or risk factors with normal LVEF</td>
<td>Treat and monitor LVEF every 3 months</td>
</tr>
<tr>
<td></td>
<td>B. Cardiac history and/or risk factors with normal LVEF</td>
<td>Treat. Ask about symptoms and perform thorough PE before each cycle</td>
</tr>
<tr>
<td></td>
<td>C. Decreased LVEF</td>
<td>Measure troponin level after therapy and BNP level before next cycle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treat low EF (ACE-I or ARB, BB) and remeasure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individual decisions about initiating trastuzumab</td>
</tr>
</tbody>
</table>
During Trastuzumab-Based Therapy

<table>
<thead>
<tr>
<th>During trastuzumab-based therapy</th>
<th>First decrease in LVEF</th>
<th>Second decrease in LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trastuzumab holiday for 1 mo
A. Treat HF and remeasure
   1. Return to baseline. Restart trastuzumab
   3. If LVEF remains low: individual decisions

A. Stop trastuzumab
B. If trastuzumab only option: "Holiday" and maximize HF Rx
Completion of Trastuzumab-Based Therapy

Completion of trastuzumab-based therapy

- No change in LVEF and no symptoms during treatment
- LVEF decreased or symptoms

- No monitoring post treatment completion
- Continue HF treatment
- Monitor according to clinical practice for HF
Anthracyclines
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

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.

Cancer March 1967

Acute and sub-acute cardiotoxicity are rare
ECG changes
Acute and sub-acute cardiotoxicity are rare ECG changes
Frequency of Cardiotoxicity

• **Doxorubicin** - 3% at 400 mg/m², 7% at 500 mg/m² and 18% at 700 mg/m².

• **Epirubicin** - less cardiotoxic - up to 900 mg/m² before cardiotoxicity limits further therapy.

• However, it tends to be given at 25-50% higher to achieve similar anticancer benefit.

• There is considerable variation between patients in their susceptibility to anthracycline-induced cardiotoxicity
Cardiotoxicity - Mechanism

[Diagram of cardiotoxicity mechanism involving various pathways and molecules such as DOX, ROS, NOS, and mitochondrial dysfunction.]
Risk Factors

- Age (young children and the elderly)
- Chest wall radiation
- Female
- Use in combination with other potentially cardiotoxic antineoplastic agents
- Previous CVD
- HTN
Prevention

• Monitoring!
• Total cumulative anthracycline dose
• New anthracycline analogues
• Protracted infusions
• Drug formulations (liposome encapsulation)
• Concomitant protective drugs
• Adequate selection of patients
Monitoring & Follow Up

- No clear guidelines from any expert group on the frequency or optimal method of LVEF assessment, or the best parameter to follow.
- Echo
- Radionuclide angiography (first pass or MUGA)
- C-MRI ?!
Cardiac Biopsy

- *loss of myofibrils and the vacuolization of cytoplasm characteristic of doxorubicin induced myopathy*
Cardiac Biomarkers

- A decrease in LVEF - a marker of advanced damage
- Early indication of cardiac damage and increased risk for a cardiac event:
  - Serum troponins:
    - Elevations in troponin I may be an early marker of acute myocardial injury.
  - BNP
Cardiac troponins predict left ventricular dysfunction from chemotherapy

204 pts

TnI after every single cycle of HDC

echo -7 m

in the cTnI+ group
LVEF reduction was more marked and still evident at the end of the follow-up

Cardinale et al. J Am Coll Cardiol 2000
Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

Daniela Cardinale, MD; Maria T. Sandri, MD; Alessandro Colombo, MD; Nicola Colombo, MD; Marina Boeri, MD; Giuseppina Lanantia, MD; Maurizio Civelli, MD; Fedro Peccatori, MD; Giovanni Martinelli, MD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

703 cancer pts
TnI soon after CT (early TnI)
1 month later (late TnI)

Echo
0,1m,2m,6m,12m,18m,24m

f/u 20 m

Circulation. 2004;109:2749-2754
Persistently increased NT-proBNP early after administration of HDC is strongly associated with development of cardiac dysfunction.

Clinical Chemistry 51, No. 8, 2005

52 pts
NT-proBNP measurements: 0, 12h, 36h, 72h, echo 1 y
Cardiac Monitoring

<table>
<thead>
<tr>
<th>Anthracycline cumulative dose (mg/m²*)</th>
<th>Pre-treatment</th>
<th>During treatment</th>
<th>At end of treatment</th>
<th>First year following treatment</th>
<th>Years 2–5 following treatment</th>
<th>&gt;Year 5 following treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>Yes</td>
<td>As clinically indicated</td>
<td>Yes</td>
<td>Follow-up at 1 year</td>
<td>Follow-up at 2 years and at 5 years</td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>200–300</td>
<td>Yes</td>
<td>After 200 mg/m²</td>
<td>Yes</td>
<td>Follow-up at 6 months and at 1 year</td>
<td>Follow-up at 2 years, 3 years and at 5 years</td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>300–400</td>
<td>Yes</td>
<td>After 200, 300 and 350 mg/m²</td>
<td>Yes</td>
<td>Follow-up at 6 months and at 1 year</td>
<td>Follow-up annually</td>
<td>Follow-up every 2 years</td>
</tr>
<tr>
<td>&gt;400</td>
<td>Yes</td>
<td>After 200, 300, 350 and 400 mg/m²</td>
<td>Yes</td>
<td>Follow up at 3 months, 6 months and at 1 year</td>
<td>Follow-up annually</td>
<td>Follow-up annually</td>
</tr>
</tbody>
</table>

*Cumulative doses are given for doxorubicin; for mitoxantrone multiply dose by 0.2, for epirubicin and liposomal preparations multiply dose by 1.5.

For patients at increased cardiac risk, a more aggressive monitoring schedule is appropriate.
FDA-approved Labeling Guidelines for Adriamycin

• In adults, a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45%, or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function.

• The benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage.
Prevention

- Monitoring!
- Total cumulative anthracycline dose
- New anthracycline analogues
- Protracted infusions
- Drug formulations (liposome encapsulation)
- Concomitant protective drugs
- Adequate selection of patients
Reduced Cardiotoxicity of Doxorubicin by a 6-Hour Infusion Regimen
A Prospective Randomized Evaluation

J. SHAPIRA, MD, M. GOTFRIED, MD, M. LISHNER, MD, AND M. RAVID, MD

**Table 1.** Doxorubicin Cardiotoxicity: Comparison Between Standard Short Infusion and 6-Hour Infusion*

<table>
<thead>
<tr>
<th>Doxorubicin Infusion</th>
<th>No. of Patients</th>
<th>Age (yr)</th>
<th>Doxorubicin Total Dose (mg/m²)</th>
<th>LVEF Initial</th>
<th>After 300 mg/m² doxorubicin</th>
<th>Percent of Change (range)</th>
<th>QRS in Standard Leads Percent of Change (range)</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–20 mins 8 am</td>
<td>28</td>
<td>55 ± 14</td>
<td>410 ± 42</td>
<td>0.6 ± 0.03</td>
<td>0.48 ± 0.05</td>
<td>−17 ± 5 ($–7$ to $–35$)</td>
<td>−29 ± 7 ($–22$ to $–68$)</td>
<td>4</td>
</tr>
<tr>
<td>360 mins 8 am–2 pm</td>
<td>30</td>
<td>53 ± 12</td>
<td>428 ± 48</td>
<td>0.61 ± 0.03</td>
<td>0.58 ± 0.05</td>
<td>−4 ± 6 ($–5$ to $–8$)</td>
<td>−5 ± 8 ($–28$ to $–47$)</td>
<td>0</td>
</tr>
</tbody>
</table>

LVEF: left ventricular ejection fraction; CHF: congestive heart failure. * All values are given as mean ± standard deviation.

Figure 4 Clinical and subclinical cardiotoxicity in RCTs where cardiotoxicity outcomes could not be categorised as one or the other. The open diamond represents the pooled Peto Odds Ratio and 95% CI for treatment comparisons 1, 2 and 4, and relative risk (RR) with 95% CI for comparisons 5-7. I-squared represents the proportion of variability between studies in excess of that expected due to chance, and p = probability that differences between study estimates are due to chance.

Smith et al. BMC Cancer 2010, 10:337
Liposomal Doxorubicin

• non-pegylated liposomal doxorubicin (Myocet)

• pegylated liposomal doxorubicin (Caelyx, Doxil)
Treatment

• Prevention
  – Beta blockers
  – ACEI

• Cardiomyopathy
  – Beta blockers
  – ACEI
  – Withdrawl
  – Reversibility ? (!)
Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy

Nihat Kalay, MD,* Emrullah Basar, MD,* Ibrahim Ozdogru, MD,* Ozlem Er, MD,† Yakup Cetinkaya, MD,* Ali Dogan, MD,* Tugrul Inanc, MD, Abdurrahman Oguzhan, MD,* Namik Kemal Eryol, MD,* Ramazan Topsakal, MD,* Ali Ergin, MD*

Figure 1. Comparison of left ventricular ejection fraction (EF) at baseline (black bars) and after chemotherapy (white bars) in the 2 groups. Data expressed as mean values.

ANT therapy, carvedilol vs placebo
25 pts, 12.5 mg
f/u 6 m
Echo baseline, 6m

J Am Coll Cardiol 2006;48:2258–62
Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Daniela Cardinale, MD; Alessandro Colombo, MD; Maria T. Sandri, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Maurizio Civelli, MD; Giovanni Martinelli, MD; Fabrizio Veglia, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

114 pts HDC
Early TnI ↑
ACEI (enalapril 20 mg); placebo f/u 12 m

Figure 1. LVEF at baseline and during the 12-month follow-up in control subjects (left) and the ACEI group (right) in patients with (■) or without (□) persistent TnI increase. For treatment effect, P<0.001; for effect of persistent TnI increase, P<0.001; for interaction between treatment and persistent TnI increase, P<0.001. R indicates randomization. *P<0.001 vs baseline and randomization for all time points; #P<0.001 vs patients without persistent TnI increase.
Treatment

• Prevention
  – Beta blockers
  – ACEI

• Cardiomyopathy
  – Beta blockers
  – ACEI
  – Withdrawal
  – Reversibility ? (!)
## Treatment of CT-induced CMP

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>N. pts</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefrak</td>
<td>Cancer</td>
<td>1973</td>
<td>2</td>
<td>Digitalis + Diuretics</td>
</tr>
<tr>
<td>Cohen</td>
<td>Arch Intern Med</td>
<td>1982</td>
<td>1</td>
<td>Digitalis + Diuretics</td>
</tr>
<tr>
<td>Haq</td>
<td>Cancer</td>
<td>1985</td>
<td>43</td>
<td>Digitalis + Diuretics</td>
</tr>
<tr>
<td>Saini</td>
<td>Ann Intern Med</td>
<td>1987</td>
<td>3</td>
<td>ACEI</td>
</tr>
<tr>
<td>Jensen</td>
<td>Lancet</td>
<td>1996</td>
<td>8</td>
<td>ACEI</td>
</tr>
<tr>
<td>Fazio</td>
<td>Clin Cardiol</td>
<td>1998</td>
<td>1</td>
<td>Beta-Blockers</td>
</tr>
<tr>
<td>Noori</td>
<td>J Card Fail</td>
<td>2000</td>
<td>10</td>
<td>ACEI + Beta-Blockers</td>
</tr>
<tr>
<td>Jensen</td>
<td>Ann Oncol</td>
<td>2002</td>
<td>10</td>
<td>ACEI</td>
</tr>
<tr>
<td>Mucai</td>
<td>Intern Med</td>
<td>2004</td>
<td>5</td>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Tallaj</td>
<td>Heart Lung Transplant</td>
<td>2005</td>
<td>25</td>
<td>ACEI + Beta-blockers</td>
</tr>
<tr>
<td>Ajijola</td>
<td>Am J Cardiol</td>
<td>2008</td>
<td>4</td>
<td>ACEI + Beta-blockers</td>
</tr>
</tbody>
</table>

**Total**: 112
• 201 pts with AC-induced CMP (baseline LVEF 37±28 %)
• 148 women (74%)
• mean follow-up: 36±27 months (range 12-96)
• enalapril (36%); enalapril + carvedilol (71%)
• Responders: LVEF ≥50% from baseline
• Partial Responders: LVEF <50% +10 abs. points
• Non Responders: LVEF <50% <10 abs. points
<table>
<thead>
<tr>
<th>Clinical characteristics of the three study groups.</th>
<th>Responders (n=85; 42%)</th>
<th>Partial Responders (n=26; 13%)</th>
<th>NON Responders (n=90; 45%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>52±12</td>
<td>53±12</td>
<td>54 13</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>65 (776)</td>
<td>21 (81%)</td>
<td>63 (70%)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>27 (32%)</td>
<td>6 (23%)</td>
<td>24 (27%)</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>5 (6%)</td>
<td>2 (8%)</td>
<td>10 (11%)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>6 (7%)</td>
<td>3 (11%)</td>
<td>10 (11%)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Current or past smokers</strong></td>
<td>32 (38%)</td>
<td>10 (38%)</td>
<td>33 (37%)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Family history of CAD</strong></td>
<td>11 (13%)</td>
<td>5 (19%)</td>
<td>10 (11%)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>NYHA class III-IV</strong></td>
<td>11 (13%)</td>
<td>18 (69%)</td>
<td>24 (27%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LVEF before AC therapy</strong></td>
<td>62 4</td>
<td>60 4</td>
<td>60 4</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>LVEF before HF therapy</strong></td>
<td>41 5</td>
<td>28 4</td>
<td>38 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Time-To-HF-Treatment (months)</strong></td>
<td>2 (1-3)</td>
<td>4 (2-6)</td>
<td>17 (8-36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>HF therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Enalapril + Carvedilol</strong></td>
<td>67 (78%)</td>
<td>13 (50%)</td>
<td>49 (54%)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>21 (25%)</td>
<td>18 (69%)</td>
<td>49 (50%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>0 (0%)</td>
<td>4 (9%)</td>
<td>8 (9%)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td>1 (1%)</td>
<td>2 (8%)</td>
<td>5 (6%)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Cumulative AC dose (mg/m²)</strong></td>
<td>301 124</td>
<td>341 130</td>
<td>222 150</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Creatinine clearance (ml/min)</strong></td>
<td>106 42</td>
<td>107 42</td>
<td>95 27</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Mean follow-up duration (months)</strong></td>
<td>34 26</td>
<td>46 30</td>
<td>36 27</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Cancer death during follow-up</strong></td>
<td>23 (27%)</td>
<td>9 (35%)</td>
<td>30 (33%)</td>
<td>0.60</td>
</tr>
</tbody>
</table>
The more time passes, the less is the possibility of recovery.
Cumulative cardiac events during study follow-up.

CONSIDERED EVENTS:
- Sudden death
- Cardiac death
- Acute pulmonary edema
- Heart failure
- Life-threatening arrhythmias
- PM implantation

P = 0.0003 (Log Rank Test)
Under Investigation:

Erythropoietin improves myocardial performance in doxorubicin-induced cardiomyopathy

European Heart Journal (2006)

Saher Hamed¹, Iris Barshack¹, Galia Luboshits¹, Dov Wexler¹, Varda Deutsch², Gad Keren¹, and Jacob George¹

The protective roles of nitric oxide and superoxide dismutase in adriamycin-induced cardiotoxicity

Cardiovascular Research 69 (2006)

Marsha P. Cole a, Luksana Chaiswing b,c, Terry D. Oberley b, Stephanie E. Edelmann d, Michael T. Piascik d, Shu-Mei Lin a, Kinsley K. Kinningham e, Daret K. St. Clair a,*

Adenosine A₃ receptor-mediated cardioprotection against doxorubicin-induced mitochondrial damage


Avishag K. Emanuelov a, Asher Shainberg a, Yelena Chepurko b, Doron Kaplan c, Alex Sagie a, Eyal Porat d, Michael Arad e, Edith Hochhauser b,*
Phospholipase C-δ1 Is a Critical Target for Tumor Necrosis Factor Receptor–Mediated Protection against Adriamycin-Induced Cardiac Injury

Yu-Chin Lien,1 Teresa Noel,1 Hua Liu,2,4 Arnold J. Stromberg,2,4 Kuey-Chu Chen,3,4 and Daret K. St. Clair1

Cancer Res 2006

Phosphodiesterase-5 Inhibition With Sildenafil Attenuates Cardiomyocyte Apoptosis and Left Ventricular Dysfunction in a Chronic Model of Doxorubicin Cardiotoxicity

Patrick W. Fisher, DO; Fadi Salloum, BS; Anindita Das, PhD; Haroon Hyder, MD; Rakesh C. Kukreja, PhD

Circulation April 5, 2005
General Approach

Cardio-Oncology Collaboration
New cardiologic approach?

- sex
- age
- family history for CAD
- smoking
- hypertension
- diabetes
- dyslipidemia
- obesity
- sedentariness

- chemotherapy!
Chemotherapy as CV risk factor!!

Treatment-Specific Risks of Second Malignancies and Cardiovascular Disease in 5-Year Survivors of Testicular Cancer

Purpose
To compare radiotherapy and chemotherapy effects on long-term risks of second malignant neoplasms (SMNs) and cardiovascular diseases (CVDs) in testicular cancer (TC) survivors.

Patients and Methods
In our nationwide cohort comprising 2,707 5-year TC survivors, incidences of SMNs and CVDs were compared with general-population rates by calculating standardized incidence ratios (SIRs) and absolute excess risks (AERs). Treatment effects on risks of SMN and CVD were quantified in multivariable Cox regression and competing risks analyses.

Results
After a median follow-up time of 17.6 years, 270 TC survivors developed SMNs. The SIR of SMN overall was 1.7 (95% CI, 1.5 to 1.9), with an AER of 32.3 excess occurrences per 10,000 person-years. SMN risk was 2.6-fold (95% CI, 1.7- to 4.0-fold) increased after subdiaphragmatic radiotherapy and 2.1-fold (95% CI, 1.4- to 3.1-fold) increased after chemotherapy, compared with surgery only. Subdiaphragmatic radiotherapy increased the risk of a major late complication (SMN or CVD) 1.8-fold (95% CI, 1.3- to 2.4-fold), chemotherapy increased the risk of a major late complication 1.9-fold (95% CI, 1.4- to 2.5-fold), and smoking increased the risk of a major late complication 1.7-fold (95% CI, 1.4- to 2.1-fold), compared with surgery only. The median survival time was 1.4 years after SMN and 4.7 years after CVD.

Conclusion
Radiotherapy and chemotherapy increased the risk of developing SMN or CVD to a similar extent as smoking. Subdiaphragmatic radiotherapy strongly increases the risk of SMNs but not of CVD, whereas chemotherapy increases the risks of both SMNs and CVDs. Prolonged follow-up after chemotherapy is needed to reliably compare the late complications of radiotherapy and chemotherapy after 20 years.

Diagnosis of Acute Myocardial Infarction

- Chest Pain
- EKG
- 1960
- AST
- LDH
- 1970
- CK activity
- 1980
- CKMB mass
- 1990
- Troponins
- 2000
- hSTroponins?
- 2010

mortality
EARLY DETECTION OF CARDIOTOXICITY

LVEF

Cardiac biomarkers

Late changes:
- LVEF evaluation (ECHO, MUGA)
- Endomyocardial biopsy

Cancer treatment

Baseline

Lower limit of normal

Early diagnosis

Late diagnosis

Time

The Leviev Heart Center
• Cardiotoxicity and increased CV risk are potentially serious complications of chemotherapy.

• Cardiotoxicity is becoming increasingly important in the modern medical practice in parallel with the ever-expanding number of treated cancer patients and growing complexity and toxicity of oncologic treatments.
• Cardiologists should be involved early in the management of cancer patients eligible for antitumoral treatment in joint collaboration with oncologists.

• Guidelines regarding cardiotoxicity should be updated by oncologists and cardiologists together, in order to optimize the management of cancer patients, and improve both oncologic and cardiologic outcome.
January 2009: The International CardiOncology Society is born.
Thank you for your attention!!!