Cancer therapeutics – related cardiac dysfunction
The role of Echocardiography

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University Hospital Of Patras
Cardio-oncology: an increasingly relevant issue

Cancer incidence by age (1995-97)


More subjects will have both CV disease and cancer

Merrill RM Annals Epidemiol 2001

AHA statistical update 2011; Circulation 2011
Cardio - oncology: an increasingly relevant issue

The CV impact of cancer treatments

- Longer survival - long term side effects – older patients
- More drugs, more cardiotoxicity
- More aggressive treatments

Figure 2. Estimated number of cancer survivors in the United States from 1971 to 2008 (23).
Breast cancer and CV death in large registries

63566 women > 65 years

CVD disease leading cause of death overall

Patnaik JL Breast Cancer Res 2011
# The cardiotoxic effects of cancer treatments - chemotherapies

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Generic</th>
<th>Site</th>
<th>Cardiac adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Doxorubicine, epirubicine...</td>
<td>Gyn blood, lung</td>
<td>CHF</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Cicplatine</td>
<td>Ov, sarcomas, lung lymphomas, blood</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digestive</td>
<td>Ischemia CHF</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Cyclophosphamide</td>
<td>Lung, ov, breast...</td>
<td>Myocarditis CHF</td>
</tr>
<tr>
<td>Antimicrotubules</td>
<td>Flourouracil</td>
<td>Kindey, melanoma...</td>
<td>Ischemia</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Paclitaxel</td>
<td>Blood, melanoma...</td>
<td>Coduction CHF</td>
</tr>
<tr>
<td></td>
<td>Interleukines</td>
<td>Metastatic GI</td>
<td>Hypot, arrhythmia</td>
</tr>
<tr>
<td>Monoclonal</td>
<td>Interferone-a</td>
<td>metastatic lung</td>
<td>Hypotension CHF</td>
</tr>
<tr>
<td>antibodies</td>
<td>Bevacizumab</td>
<td>Breast (HER2+)</td>
<td>Hypertension CHF</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Transtuzumab</td>
<td>CML, GI tumors</td>
<td>CHF</td>
</tr>
<tr>
<td></td>
<td>Imatimibe</td>
<td></td>
<td>CHF per effusion</td>
</tr>
</tbody>
</table>

Yeh T.H et al Circulation 2004
UNDERLYING CAUSES AND LONG-TERM SURVIVAL IN PATIENTS WITH INITIALLY UNEXPLAINED CARDIOMYOPATHY

Proportion of Patients Surviving

0.00 0.25 0.50 0.75 1.00

Years

0 2 5 10 15

2 years

Peripartum cardiomyopathy
Idiopathic cardiomyopathy
Cardiomyopathy due to doxorubicin therapy
Cardiomyopathy due to infiltrative myocardial disease
Cardiomyopathy due to ischemic heart disease
Cardiomyopathy due to HIV infection

Felker GM NEJM 2000
Mechanisms and Models in Heart Failure

- Index Event
- Ejection Fraction
  - 60%
  - 20%
- Secondary Damage
- Compensatory Mechanisms
- Asymptomatic → Symptomatic
- Time (yrs) →

Mann D Circulation 1999
## Risk factors for the development of 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)</td>
</tr>
<tr>
<td>Cardiac irradiation</td>
<td>NA</td>
<td>Steinherz et al. (1991)</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>1.53</td>
<td>Hershman et al. (2008)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.58</td>
<td>Hershman et al. (2008)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.21</td>
<td>Hershman et al. (2008)</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td>2.25</td>
<td>Swain et al. (2003)</td>
</tr>
</tbody>
</table>

Ewer MS and Ewer SM Nature Rev. Cardiology 2010
Cancer therapeutics – related cardiac dysfunction

**Type I CTRCD**
- Cellular death
- Biopsy changes
- Cumulative dose-related
- Permanent damage

Model: Doxorubicin

**Type II CTRCD**
- Cellular dysfunction
- No biopsy changes
- Not cumulative dose-related
- Reversible

Model: Trastuzumab (Herceptin)
Cancer therapeutics – related cardiac dysfunction

- Decrease in the LVEF of greater than 10 percentage points to a value below the reference value of normal (symptomatic or asymptomatic)

\[
\text{EF} = 63 \pm 5 \%
\]

Normal \( \text{EF} = 53 - 73 \% \)

Plana JC, Galderisi M et al. ASE/EACVI recommendation 2014
Anthracycline-Induced Cardiomyopathy

Clinical Relevance and Response to Pharmacologic Therapy

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

AC = anthracyclines; HF = heart failure.

Cardinale D et al JACC 2010
Figure 2
Cumulative Cardiac Event Rate During the Study Follow-Up

2-year Kaplan-Meier analysis for major adverse cardiac events in the 3 study groups. p = 0.0003 (log-rank test).

Cardinale D et al JACC 2010
After chemotherapy LVEF = 35%

After CHF therapy LVEF = 55%
Limitations of 2D Echo derived LVEF for detection of Cardiotoxicity

Geometrical assumptions made in its calculation.

Possibility of inadequate visualization of the true apex of the LV

Inherent variability of the measurement

Low sensitivity for early detection of cardiotoxicity
Reproducibility of Echocardiographic Techniques for Sequential Assessment of Left Ventricular Ejection Fraction and Volumes

Application to Patients Undergoing Cancer Chemotherapy

Paaladinesh Thavendiranathan, MD, MSc, Andrew D. Grant, MD, Tomoko Negishi, MD, Juan Carlos Plana, MD, Zoran B. Popović, MD, PHD, Thomas H. Marwick, MD, PHD, MPH

Cleveland, Ohio

3D Echo was the most reproducible technique for LVEF and Volume measurements

Minimal detectable change (CI 95%) in EF was 6%

With 2D Echo the minimal detectable change (CI 95%) in EF was 10% (cut-off point that defines cardiotoxicity)
3D volumes and EF – Comparison with MRI

- **LVEDV**
  Bias  -9.9 ml (-11.8 to -8)

- **LVESV**
  Bias  -4.7 ml (-5.6 to -3.7)

- **LVEF**
  Bias  -0.13% (-0.45 to 0.18)

95 studies, 3055 pts with 3D vs CMR

Shimada Y, Shiota T Am J Cardiol 2011
Limitations of 3D Echo derived LVEF for detection of Cardiotoxicity

- Availability (echo machines)
- Feasibility in cancer patients (lower than 2D echo)
- Low sensitivity for early detection of cardiotoxicity (same as 2D echo)
Speckle tracking echocardiography: Non Doppler strain
Different strain for differed fibers

Longitudinal strain for subendocardial fibers (most sensitive in heart diseases), measured locally and globally

Radial strain

Circumferential strain

Midwall and subepicardial fibers
546 pts undergoing echo for LV function. 91 died over 5.2 ± 1.5 years

GLS provided incremental value in pts with EF > 35% and without WMA

Stanton T Circ Cardiovasc Imaging 2009
LV strain precedes EF change in animals

20 mice treated with multiple doses of DOX for 5 weeks

Survival was 100%, 95% and 35% at 6, 12, and 16 weeks after 1st dose

DOX caused early LV dysfunction with preservation of EF

Table 4 Early (6 weeks) echocardiographic parameters in animals separated according to survival at termination of study (n = 20)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alive (n = 7)</th>
<th>Deceased (n = 13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{ENDO}$ (cm/s)</td>
<td>2.9 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SR (s⁻¹)</td>
<td>17.6 ± 1</td>
<td>13.5 ± 1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVIDd (mm)</td>
<td>3.6 ± 0.1</td>
<td>3.5 ± 0.1</td>
<td>0.64</td>
</tr>
<tr>
<td>LVIDs (mm)</td>
<td>1.6 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>0.43</td>
</tr>
<tr>
<td>FS (%)</td>
<td>55 ± 1</td>
<td>55 ± 1</td>
<td>0.52</td>
</tr>
<tr>
<td>EF (%)</td>
<td>78 ± 1</td>
<td>76 ± 1</td>
<td>0.27</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>625 ± 12</td>
<td>613 ± 14</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Twenty animals were treated with 4 mg/kg of DOX per week for 5 weeks, beginning at day 0. Seven animals survived to termination of study at 4 months.

Neilan TG Heart 2006
Global longitudinal strain for prediction of Cardiotoxicity

81 breast cancer women treated with ANT+TAX+ TRAST FU 15 months

32% developed cardiotoxicity 6% of them with symptoms

A GLS < 19% at 3 months (end of ANT therapy) was the only independent predictor of subsequent cardiotoxicity

A decrease of GLS > 10% from baseline was also predictive of subsequent cardiotoxicity

LVEF and change in LVEF at the end of therapy was not

Sawaya H et al Circ Cardiovasc Imaging 2012
Global longitudinal strain for prediction of Cardiotoxicity

81 breast cancer woman (37 with concomitant ANT) receiving trastuzumab. 30% of them developed cardiotoxicity (>10% drop of LVEF in 12 months).

A decrease from baseline of GLS at six months was the best predictor of subsequent cardiotoxicity. The optimal cut-off was $\Delta GLS \geq 11\%$

Negishi K JASE 2013
Early detection of Cardiotoxicity using GLS

10 points drop to LVEF < 53% → Cardiotoxicity

Baseline GLS available

No → Baseline GLS unavailable

Relative drop < 8% as compared to baseline → No subclinical dysfunction

Relative drop > 15% as compared to baseline

Subclinical dysfunction

< -19% during treatment

No subclinical dysfunction

> -19% during treatment

No subclinical dysfunction

Plana JC, Galderisi M et al
ASE/EACVI recommendations 2014
GLS = -19.9%
What can we do with this information?

- 159 pt receiving cardiotoxic chemotherapy
- 33% of them developed abnormal ΔGLS > 11%

Recovery of cardiac function (EF and GLS) with beta-blockers in patients with ΔGLS > 11% after cardiotoxic chemotherapy

Neghisi K et al. EHJ 2013
20 years old men non-Hogkin lymphoma

After anthracycline chemotherapy

GLS = -14.7%

6 months after b-b/ace-inh therapy

GLS = -22.9%
Left Ventricular Dysfunction in Patients Receiving Cardiotoxic Cancer Therapies:
Are Clinicians Responding Optimally?

J Am Coll Cardiol. 2010 November 9; 56(20):

- LVEF<55%
- Symptomatic LVEF<55%
- Asymptomatic LVEF<55%

% of Cohort

- Received ACE-I/ARB
- Received Beta-Blocker
- Cardiology Consultation
## Cardiac monitoring schedule for anthracycline therapy

<table>
<thead>
<tr>
<th>Anthracycline cumulative dose mr/m²</th>
<th>Pre-treat.</th>
<th>During treatment</th>
<th>End of treat.</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>200</td>
<td>Yes</td>
<td>As clinically indicated After 200mg/m²</td>
<td>Yes</td>
<td>At 1 year</td>
<td>At 2 and 5 years</td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>200-300</td>
<td>Yes</td>
<td>After 200,300 and 350mg/m²</td>
<td>Yes</td>
<td>At 6 months and 1 year</td>
<td>At 2,3 and 5 years</td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>300-400</td>
<td>Yes</td>
<td>After 200,300, 350 and 400 mg/m²</td>
<td>Yes</td>
<td>At 6 months and 1 year</td>
<td>Annually</td>
<td>Every 2 years</td>
</tr>
<tr>
<td>400</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>At 3 months, 6 months and 1 year</td>
<td>Annually</td>
<td>Annually</td>
</tr>
</tbody>
</table>

Ewer MS and Ewer SM Nature review Cardiology 2010
Conclusions

- Cardio-oncology will be a major growth area and a model for application of strain in clinical practise.

- Longitudinal strain predict the development of later toxicity in patients treated with chemotherapy and may be useful to select patients who could benefit from cardiovascular therapy.

- We need more cooperation between oncologists and cardiologists in order to decrease the incidence of cardiotoxicity and its associated morbidity and mortality.