Cardiotoxicity of Systemic Breast Cancer Treatment

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Cardiotoxicity of chemotherapy – a reality

- Increasing survival rates in cancer due to:
  - Best knowledge of cancer
  - Best therapeutic strategies with combination of drug regimens
  - New therapies including targeted ones

- Longer and more aggressive treatment regimens for elderly and frail patients

- Cardiac side effects of chemotherapy
  - Not restricted to anthracyclines
  - Previously unsuspected concerns with new targeted therapies
  - *At-risk patients*
Cardiotoxicity of chemotherapy – a reality

- Which drugs?
  - The best known: anthracyclines
  - Other widely used cytotoxic agents: 5-FU, cyclophosphamide, arsenic trioxide etc.
  - The majority of new biologics or so called “targeted therapies” can also contribute to cardiac side-effects

- Anti-cancer treatments are in the majority of cases
  - An association of different anti-cancer drugs
  - Repeated over time due to relapses

- What’s the need for early detection of cardiotoxicity?
  - Association of less cardiotoxic drugs?
  - Different therapeutic regimen?
  - B-blockers? ACE inhibitors?
THE MAIN TYPES OF DRUGS USED AND KNOWN TO HAVE CARDIOTOXIC EFFECTS

- ANTHRACYCLINES:
  - dose dependent
  - 2-5% HF

- TYROSINE KINASE-TARGETED THERAPIES
  - 4-7% HF
  - 10% reduction of cardiac function
Anthracyclines – Mechanism of action

Left: Normal double stranded DNA

Right: Intercalation of 3 molecules of doxorubicin (red) into double stranded DNA

Planar ring structure

Prevents the separation of the strands needed for transcription and protein synthesis. Prevents protein synthesis and further proliferation of the rapidly growing tumour cell.

Source: http://commons.wikimedia.org/wiki/File:DNA_intercalation.jpeg
Oxidative stress is believed to be secondary to the generation of oxygen-derived free radicals.

Vergely et al. Heart Metab. 2007;35:1–7
Apoptosis hypothesis

Vergely et al. Heart Metab. 2007;35:1–7
Why do anthracyclines affect the heart?

- Anthracyclines intercalate not only into nuclear DNA but also mitochondrial DNA (mtDNA):
  - Heart muscle is rich in mitochondrial DNA
- Heart muscle is susceptible to free-radical attack:
  - and deficient in protective enzymes
- Myocyte loss and ATP depletion would lead to left ventricular dysfunction and CHF
  + disruption of sarcomeres: sarcopenia
Prevalence of conventional anthracycline-induced cardiotoxicity

10–20 years after the initial oncological diagnosis:

>50% of patients show cardiac abnormalities

40% arrhythmias

5% CHF

Genetic predisposition
Cumulative dose
Dose Rate
Dosing Schedule
Concomitant treatments

These factors relate to early and late onset but not acute cardiotoxicity (Lipshultz, 2008)
## Reported cardiotoxicity of targeted anti-cancer drugs

<table>
<thead>
<tr>
<th>Drugs with a reported risk</th>
<th>Drugs with uncertain risk</th>
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<tbody>
<tr>
<td>Imatinib</td>
<td>Lapatinib</td>
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<tr>
<td>Dasatinib</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Panitumumab</td>
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<tr>
<td>Sunitinib</td>
<td>Rituximab</td>
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<tr>
<td>Sorafenib</td>
<td>Alemtuzumab</td>
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<tr>
<td><strong>Trastuzumab</strong></td>
<td>Temsirolimus</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Gefitinib</td>
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<td></td>
<td>Erlotinib</td>
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</table>
Trastuzumab (Herceptin®) targets the extracellular domain of human epidermal growth factor 2 (HER2 or ERBB2)

- Humanised monoclonal antibody
- HER2-positive breast cancer
- Interaction of trastuzumab with the ERB2 receptor leads to apoptosis:
  - via the mitochondria/cytochrome c/caspase pathway

- Results in energy loss from the cell from ATP depletion

Trastuzumab-induced cardiotoxicity

- Incidence of trastuzumab-related HF is ~2%–7%

- Increases with:
  - age >50 years
  - border-line LVEF before treatment
  - history of CVD
  - prior treatment with anthracycline

- 13% when in combination with paclitaxel

- Incidence rises to 27% when trastuzumab is used concurrently with conventional anthracycline plus cyclophosphamide

- Not dose related, idiosyncratic

- At least, partially reversible

Monsuez et al. Int J Cardiol 2010
“STARTING POINT” ON THE HEART...

CHEMOTHERAPY

1. CARDIAC MYOCYTE INJURY

2. LOSS OF MYOCYTE FUNCTION

3. ↓ CONTRACTILITY ↓ RELAXATION
   ↓ REPOLARISATION ABNORMALITIES

4. LV SYSTOLIC DYSFUNCTION
   ↓ LV DIASTOLIC DYSFUNCTION
   ↓ QT-PROLONGATION
   ARRHYTHMIAS

5. HEART FAILURE
   • DYSPNEA
   • RESTING TACHYCARDIA
   • SIGNS OF FLUID OVERLOAD
CARDIAC TOXICITY OF CHEMOTHERAPY - DEFINITION

1. TOXICITY that affects THE HEART
2. SUBCLINICAL CARDIAC DAMAGE
   - HISTOLOGY
   - BIOMARKERS
   - LV STRAIN, STRAIN RATE (deformation imaging)
3. CLINICAL CARDIAC DAMAGE
   - REDUCTION OF LVEF
   - SYMPTOMS OF HF (dyspnea, fatigue)
   - SIGNS OF HF (resting tachycardia, S3 gallop, peripheral edema, pleural effusion)
PATHOPHYSIOLOGIC CASCADE

Index Event

Compensatory Mechanisms

Ejection Fraction

Secondary Damage

Asymptomatic → Symptomatic

Time (yrs) →

60 %

20 %
Anthracycline-induced cardiotoxicity - definition

ACUTE CARDIOTOXICITY

- Rare, transient, independent of dose
- Characterised by arrhythmias (i.e. abnormal electrical activity), ECG changes, signs of acute pericarditis during or within several hours of administration
- Resolves when therapy is discontinued

EARLY ONSET CHRONIC PROGRESSIVE CARDIOTOXICITY

- Within 1 year following anthracycline administration*
- Electrophysiological changes, left ventricular dysfunction, decreased exercise capacity and clinical heart failure

LATE PROGRESSIVE CARDIOTOXICITY

- Cardiomyopathy occurring after a latency of ≥ 1 year after anthracycline treatment*
- Has a period with no LV dysfunction or arrhythmias detected
- After this latent period, there is progressive and rarely fatal deterioration in cardiac functions

*Depending on cumulative dose
Conventional monitoring for cardiotoxicity

- **Non invasive - Imaging techniques:**
  - Conventional Transthoracic Echocardiography – 2D +/- 3D, contrast echocardiography
  - Radionuclide ventriculography
  - SPECT
  - MRI

- **Non invasive – Biomarkers:** no standardized protocol
  - Troponine
  - B-type Natriuretic Peptides

- **Invasive techniques:**
  - Endomyocardial biopsy “gold standard”, sensitive, invasive, associated risks, less attractive for monitoring
Multidisciplinary approach for HER2+ in adjuvant setting

Medical history, physical examination, baseline ECG

Baseline LVEF evaluation (echocardiogram or MUGA scan)

LVEF <50%

LVEF evaluation (at end of treatment)

LVEF ≥50%

Anthracycline CT

LVEF <50%

Cardiological consult
Consider non-anthracycline CT

RISK BENEFIT ASSESSMENT

LVEF ≥50%

Trastuzumab administration

RISK BENEFIT ASSESSMENT
(add standard medical treatment for CHF)
Cardiological consult (verify LVEF reduction)

LVEF evaluation (every 3 months & as clinically appropriate); Cardiac biomarker evaluation (investigational)

Symptomatic, LVEF ≥44%

LVEF 45-49%

≥ 10 points from baseline

DISCONTINUE
(add standard medical treatment for CHF)

DISCONTINUE
Cardiological consult

LVEF evaluation after 4 weeks

LVEF ≥44% or LVEF 45-49% & ≥10 points from baseline

DEFINITE STOP

<10 points from baseline

CONTINUE

LVEF ≥49% or LVEF 45-49% & <10 points from baseline

RESUME/CONTINUE

LVEF ≥50%

LVEF ≥50%

LVEF ≥44%

LVEF evaluation every 3 months

RISK BENEFIT ASSESSMENT

Anthracycline CT
MYOCYTE INJURY

• TROPONIN RELEASE

Cell necrosis, apoptosis, increase in membrane permeability

SYSTOLIC/DIASTOLIC LV DYSFUNCTION

• BNP and NT-BNP INCREASE

Increase in LV end-systolic and/or end-diastolic wall stress

SYMP TOMS

• DEFORMATION IMAGING

RNV
ECHO 2D/3D
CONTRAST ECHO
MRI

IMAGING TECHNIQUES

• IMAGING TECHNIQUES

LVEF / FS EVALUATION

≠accuracy
Fractional shortening - Definition

- FS, MM derived echocardiography
- FS = (LVIDD-LVIDS)/LVIDD
- FS = 30-42%, normal

LVEF (Teichholtz)

Ask the sonographer/cardiologist to indicate if LVH present
If LVH do not rely on FS!!!
LV ejection fraction - definition

- Indirect measurement of LV systolic function, still the most widely used

- Not the best

- It measures the LV cavity reduction in systole normalized for end-diastolic volume

- Preserved LVEF > 50%

- LVEF:
  \[
  \text{LVEF} = \frac{\text{LVEDV} - \text{LVESV}}{\text{LVEDV}}
  \]
Caveats in measuring LV ejection fraction

- Image-quality dependent

Other methods for LVEF assessment

- Contrast Echocardiography
- Cine MRI
- Cineventriculography

Ultrasonographers should report this information in the echo protocol!
Ask them !!!
Caveats in measuring LV ejection fraction

- measurement variability (intra and inter-observer)

**Same ultrasonographer**

Your patient under anthracycline therapy:

Baseline: LVEF=52% (d. dr A)

**GO ON!**

After 1st session: LVEF=49%

**STOP!**

LVEF=39%

Δ 3%

Δ 14%

LVEF=24%

LVEF=27%

LVEF=63%
3D-echo LVEF?

- Better than 2D!
- Well validated
- 30% poor image quality
- Underestimation/MRI
- Availability?
MRI

- Reproducibility
- Essential to include trabeculae
- High cost
- Availability
- Not sufficient for early diagnosis
- Not predictive
Caveats in measuring LV ejection fraction

If you decide on monitoring LVEF... use the same method, they are not equivalent!

LV Volumes

MRI

Contrast Echo

Conventional Echo

LVEF

Baseline

-------

After ChTx

LVEDV

LVESV

LVEF

50%

56%

70%
Methods with higher sensibility in detecting subtle changes in LV systolic function

*Tissue Doppler, Speckle Tracking and their derivatives*

2D Speckle Tracking
- rotation and deformation -

Tissue Velocity Imaging
- velocities -

Normal LVEF and FS

Identify subclinical LV dysfunction
Tissue Velocity Imaging - velocities -

- Animal model
- 20 mice, 1 dose DOX 20mg/kg
- LVEF, FS, $V_{ENDO}$ (peak endocardial systolic velocity), SR baseline, day 1-5

Neilan et al. Eur Heart J, 2006
Tissue Velocity Imaging

- *strain* -

16 patients, normal LVEF

6 cycles of DOX

Conventional echo and TDI

–baseline; 3M and 6M

Strain and SR allow the detection
Of subtle changes in longitudinal
And radial LV function
**Tissue Velocity Imaging - strain -**

<table>
<thead>
<tr>
<th>At 3 Months</th>
<th>No CTx (n=34)</th>
<th>CTx (n=9)</th>
<th>p</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ LVEF</td>
<td>1.2±9</td>
<td>5.6±8</td>
<td>0.19</td>
<td>5.5</td>
</tr>
<tr>
<td>Δ GLS</td>
<td>3±10</td>
<td>15±8</td>
<td>0.01</td>
<td>500</td>
</tr>
<tr>
<td>Δ RS</td>
<td>2±23</td>
<td>22±22</td>
<td>0.02</td>
<td>250</td>
</tr>
<tr>
<td>Nt-proBNP</td>
<td>46±240</td>
<td>56±190</td>
<td>0.91</td>
<td>1</td>
</tr>
<tr>
<td>↑ Hs-Tnl</td>
<td>6 (18%)</td>
<td>6 (67%)</td>
<td>0.006</td>
<td>9</td>
</tr>
</tbody>
</table>

**43 patients, Anthra+TZB, Echo: baseline, 3M and 6M, 9 patients (21%) with proven Ctx**

**Prediction of Ctx by:** ↓ L-strain at 3M, ↑ hs Tn at 3M; Not LVEf, diastolic function or BNP

Sawaya et al. Am J Cardiol, 2011
3D speckle tracking

- Not enough information or experience
Myocardial deformation imaging can detect subtle changes in LV systolic function

- TROPONIN RELEASE
- BNP and NT-BNP INCREASE
- DEFORMATION IMAGING
- LVEF / FS EVALUATION

Index event = myocyte damage

Ejection fraction (%)

50%

No Symptoms
LV dysfunction (subclinical)

No Symptoms

Symptoms

Time (years)

LVEF and strain are load-dependent!

Adapted after Mann D L. Circulation 1999
Role of biomarkers
- Troponin and BNP -

HDC (3 months)  

211 Patients

HDC 3 months

Tn I evaluation

Tn I +  
(≥0.5ng/ml)

Tn I -  
(<0.5ng/ml)

p<0.001

Cardinale et al, Ann Oncol 2002
Role of biomarkers
- Troponin and BNP -

WHO? HOW? WHEN?

• At-risk patients:
  • > 65 y
  • Previous cardiomyopathy, LVH, CHD, diabetes
  • Smoking
  • Obesity
  • Metastatic disease
  • Cumulative dose of anthracycline > 400 mg/m²
  • Dosing schedule
  • Radiotherapy > 20 Gy
  • Association with cyclophosphamide, trastuzumab, taxanes
  • Co-administration of potentially cardiotoxic agents
WHO? HOW? WHEN?

- Check-up prior to chemotherapy
- Aggressive early treatment of CV risk factors

LVEF :
  - Echo : Teichholtz, Simpson (2D), contrast, 3D
  - Isotopic ventriculography
  - MRI

Strain : GLS, SR

Bio-markers : Tn, BNP, NT-pro-BNP : when ? How frequently ?

Chemotherapy ?

Cardiac treatment : β-blockers? ACEI (Herceptine)?
Follow-up:

+ 3, 6 weeks
+ 3, 6 months

Anthracycline:

• $\geq 400 \text{ mg/m}^2 : 1/\text{y}$
• 200-300 $\text{mg/m}^2 : 1/\text{y}$ during 5 y, then 1 every 2 y
• $< 200 \text{ mg/m}^2 : 1$ every 2 y
PATIENT “at risk”

**ONCOLOGIST**
- Assess need for potential CTx treatment
- Assess the initial risk (type of drug, regimen, clinical characteristics)
- Reassess risk and benefit in function of CV status
- Decide treatment

**CARDIOLOGIST**
- Explain risk + need for CTx treatment
- Explain the patient’s CV status
- Baseline cardio evaluation (clinical, ECG)
- Established CV disease (severity, treatment)
- Baseline echo study (LVH, FS, LVEF, LV strain)
- Decide if baseline study satisfactory for FUP (MRI? Contrast Echo?)
- Decide if FUP by Tn, BNP

**ONCOLOGIST**
- Ask about LVH, image quality baseline study
- Inform about limitations of FUP techniques

**CARDIOLOGIST**
- Decide if FUP by Tn, BNP

**ONCOLOGIST**
- Decide together
Teamwork is essential

Are you convinced?

THANK YOU!
Anthracyclines – Mechanism of action

(dsDNA in supercoiled form)

Topoisomerase separates and cleaves the dsDNA strands

Interaction with anthracycline forms a stable ternary complex preventing the resealing of the DNA break

Topoisomerase reseals the DNA strands in a different place to liberate the 2 daughter strands for replication
What are we looking for?

LV dysfunction (systolic and/or diastolic) +/- CHF

Anthracyclines
- Taxanes
- Alkylation agents

Tyrosine kinase-targeted therapies

CAD (myocardial ischemia/infarction)

Hypertension

Arrhythmias/QT prolongation
LVEF fails to detect cardiac toxicity at an early stage

- Dependent on image quality in echo
- Dependent on operator (both MRI and echo)
- Absolute value dependent on the technique used (MRI-echo not comparable)
- Alterations of LVEF happen too late in the cascade of cardiotoxic events
- Not a measure of contractility
- Dependent on loading conditions

Index event = myocyte damage

Time (years)

Ejection fraction (%)

50%

No Symptoms
LV dysfunction (subclinical)

No Symptoms

Symptoms