Kardio-Onkologie

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Onco-Cardiology

A cardiovascular sub-specialty focused on identifying, preventing, and treating cardiovascular complications of cancer therapy

www.cancerandtheheart.org
“…you need to cure first…
…before you should be concerned about cardiotoxicity“

*Emil J. Freireich, M.D., D.Sc. Oncologist*
**Systemic Cancer Therapy Related Cardiovascular Side Effects**

- **Arrhythmia**
  - QT-Prolong

- **Cardiac Dysfunction**
  - Cardiotoxicity

- **Thromboembolism**

- **AP / MI**

- **Hypertension**

- **Pulmonary Hypertension**

- **PAOD**

- **Pleural Effusion**
SYSTEMIC CANCER THERAPY RELATED CARDIAC DYSFUNCTION/CARDIOMYOPATHY

- Arrhythmia
  - QT-Prolong

- Cardiac Dysfunction
  - Cardiotoxicity

- Hypertension

- Pulmonary Hypertension

- Thromboembolism

- PAOD

- Pleural Effusion

- AP / MI

- Systemic Cancer Therapy Related Cardiac Dysfunction/Cardiomyopathy
CARDIOVASCULAR SIDE EFFECTS OF CANCER TREATMENT

Cancer Therapy

Efficacy

Toxicity

Side Effects
Non-reversible damage type I

Pathophysiology
Cell loss (necrosis/apoptosis)

Manifestation
Cardiomyopathy / heart failure
myocardial infarction
thrombosis

Diagnosis
Injury marker release
progressive contractile dysfunction
cardiac remodeling

Progressive cardiovascular disease

Cardiovascular risk factors
(preexisting cardiac disease, hypertension, age)

Cancer therapy
(anthracyclines vs. non-anthracyclines)

Reversible dysfunction type II

Pathophysiology
Cellular dysfunction
(mitochondrial/protein dysfunction)

Manifestation
Temporary contractile dysfunction
vasospasitic angina
arterial hypertension

Diagnosis
No injury marker release
reversible contractile dysfunction
reversible arterial hypertension

Normalization of cardiovascular function

Cardiovascular therapy

Suter, T. M. and M. S. Ewer, Eur Heart J 2013; 34(15): 1102-1111
THE HEART – A POSTMITOTIC, COMPLEX ORGAN

**INTRACELLULAR SIGNAL-TRANSDUCTION PATHWAYS MODULATING CARDIAC PROTEIN SYNTHESIS**

- **GPCR**
  - ANP
  - BNP
  - Endo-1
  - Ang II
  - Catecholamines

- **Cell membrane**
  - G_{αq/α11}
  - PLC
  - Ins(1,4,5)P₃
  - DAG
  - Ca²⁺
  - Calmodulin
  - CaMK
  - PKC
  - PKG I
  - Farnesyl Transf
  - Calmodulins
  - Cellular proteins
  - Calmodulin
  - CaMK
  - HDAC 4/5/7/9
  - HDAC Inhib
  - Nucleus
  - MEF2
  - Anti HIF-1
  - Transcription factors
  - Pol II
  - NF-κB

- **Plasma membrane**
  - MAPKKK
  - MEK Inhib
  - MAPK
  - Raf Inhib
  - Ras Inhib
  - Ras
  - PI3K
  - MAPKK
  - mTOR
  - mTOR Inhib
  - AKT/PKB
  - p38
  - p38 Inhib
  - JNK
  - ERK 1/2
  - ERK 5
  - GSK3β
  - CDK 7/9
  - Pol II
  - NF-κB

- **G protein-coupled receptors (GPCRs)**
  - GPCR
  - GC-A
  - FGFR
  - RTKs
  - Tyrosine Kinase Inh
  - TGFR/Activin
  - GPCR
  - TNFR

- **Anti VEGF**
  - Anti HER2
  - Neuregulin
  - EGF
  - IGF-I
  - IGF 1 Inh
  - EGFR Inh
  - Anti VEGF
  - Tyrosine Kinase Inh
  - TGFβ
  - TGF-β Inhib
  - NFα

WHAT IS CARDIOTOXICITY?

• Heart Failure

• Cardiac Dysfunction asymptomatic
## Systemic Therapy Related Cardiac Dysfunction / Heart Failure

<table>
<thead>
<tr>
<th>Chemotherapeutics</th>
<th>Cardiac Dysfunction</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthracyclines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Doxorubicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Epirubicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td></td>
<td>1 %</td>
</tr>
<tr>
<td><strong>Signaling Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>3-18 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Lapatinib</td>
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<td>0 - 2% (9%)</td>
</tr>
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<td>Bevacizumab</td>
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</tr>
<tr>
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<td>8 -15 %</td>
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</tr>
<tr>
<td>Sorafenib</td>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Imatinib</td>
<td>2 %</td>
<td>&lt;1 %</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td></td>
<td>19-25%</td>
</tr>
</tbody>
</table>

**HER2-Inh**

**Anti-VEGF**

**Bcr-Abl**

**Prot-Inhib**
<table>
<thead>
<tr>
<th>Anthracyclines (-like)</th>
<th>Toxicity Intensifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Indarubicin</td>
<td>Mitamycin-C</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Bleomycin</td>
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</table>
Anthracycline Cardiotoxicity – Time Course

Acute Toxicity

Early Toxicity

Late Toxicity

Heart Failure Treatment (ACE-I; BB)
Cardiotoxicity of Anthracyclines

Heart Failure in RTCs

1 anthracycline (a) v non-anthracycline (b)
Ackland 2001
Feher 2005
Levine 2005
Sweetnam 1986
Subtotal (I-squared = 0.0%, p = 0.912)


Risk Factors

- Cumulative dose of doxorubicin
- Combination therapy (CT and Sig Inhibitors)
- Prior/concomitant mediastinal radiotherapy
- Age
- Previous cardiac disease
- Hypertension
- Genetic predisposition


Singal PK et al. NEJM 1998, 339, 900-5
Doxorubicin

\[ O_2^- \rightarrow H_2O_2 \]

\[ \uparrow [Ca^{2+}]_i \]

Proteases

Caspases

\[ \uparrow \uparrow [Ca^{2+}]_i \]

Protein Degradation

Protein Synthesis

Myofibrillar Disorganization

Myocyte Apoptosis

Myocyte Necrosis

Sawyer DB, Suter TM: Circulation 2002
Lim CC, Suter TM, Sawyer DB: J Biol Chem. 2004
Salvatorelli E, Minotti G: J Pharmacol Exp Ther 2013
CARDIOTOXICITY OF ANTHRACYCLINES- PREVENTION

Dose limitation
Continuous infusion
Liposomal delivery systems
Less toxic anthracyclines
Dexrazoxane
ACE inhibition
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<th>Cardiac Dysfunction</th>
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<td>4 – 15 %</td>
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</tr>
<tr>
<td>Trastuzumab (Herceptin®)</td>
<td>3-18 %</td>
<td>4 %</td>
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<td>Lapatinib (Tyverb®)</td>
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# Anti-HER2 Cardiotoxicity

## Trastuzumab (Herceptin®) Associated Cardiac Dysfunction / Heart Failure

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Heart Failure (\text{NYHA III/IV})</th>
<th>Cardiac Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31</td>
<td>3.6 %</td>
<td>15.9 %</td>
</tr>
<tr>
<td>HERA</td>
<td>0.6 %</td>
<td>3 %</td>
</tr>
<tr>
<td>BCIRG 006 A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### BCIRG 006 A
- **AC → PtX+Trast → Trast**
- **AC → Docet+Trast → Trast**
- **LVEF (%)**

#### LVEF (%)

- **B**: Cumulative Incidence (probability) vs. Time Since Random Assignment (months)
- **Observation**: 1,744 1,381 833 458 359 326 307 279 157 54
- **Trastuzumab, 1 year**: 1,082 1,486 1,355 1,262 1,211 1,183 1,129 1,061 930 190
- **Trastuzumab, 2 years**: 1,073 1,497 1,341 1,249 1,183 1,117 1,046 953 590 172

- **No. at risk**

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Kardio-Onkologie
kardio-onkologie@insel.ch
HER2 in Human Heart

<table>
<thead>
<tr>
<th>Ligands</th>
<th>EGF</th>
<th>NRG β</th>
<th>EGF R</th>
<th>ErbB2</th>
<th>ErbB4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>


REVERSIBLE CARDIAC DYSFUNCTION – CLINICAL IMPLICATIONS

HERA

LVEF ≤ 44
- Hold trastuzumab
- Repeat LVEF in 3 weeks

LVEF ≤ 44
- or
- LVEF 45-49 and ≥ 10 points from baseline
- Stop trastuzumab

LVEF 45-49 and < 10 points from baseline or LVEF > 49
- Resume trastuzumab

LVEF 45-49
- ≥ 10 EF points from baseline
- Hold trastuzumab
- Repeat LVEF in 3 weeks

LVEF ≥ 50
- Continue trastuzumab

LVEF 45-49
- < 10 EF points from baseline
- Continue trastuzumab

**PROGRESS IN CARDIO-ONCOLOGY**

### 2001 Metastatic HER2 pos


### 2005 Adjuvant HER2 pos


### 2014 Adjuvant HER2 pos


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#### Severe Heart Failure

- Metastatic HER2 pos
- HERA
- NSABP B-31
- NCCTG N 9831
- BCIRG 006_Anthra
- BCIRG 006_Taxo
- ALTTO L+T
- ALTTO T->L
- Trast

#### Card Dysfunction

- Metastatic HER2 pos
- HERA
- NSABP B-31
- NCCTG N 9831
- BCIRG 006_Anthra
- BCIRG 006_Taxo
- ALTTO L+T
- ALTTO T->L
- Trast
CV Side Effects – Prevention/Reduction

Prior RX
Risk Assessment

During Rx
Avoid Toxicity

Survivor
Surveillance
**Cardiotoxicity – Prevention/Reduction**

**Prior RX**

**Risk Assessment**

**Anthracyclines**
- Cumulative Dose
- Combination chemotherapy
- Prior/concomitant mediastinal radiotherapy
- Age
- Previous cardiac disease
- Hypertension

**Trastuzumab**
- Prior/concomitant anthra
  - Time anthra-anti HER2
- Concomitant paclitaxel?
- Age > 50 years
- Previous cardiac disease
  - Systolic Dysfunction (LVEF < 55%)
- Hypertension (medication)
- Higher BMI
CARDIOTOXICITY – PREVENTION/REDUCTION

Prior RX

Risk Assessment

- 01.13 Mamma-Ca re pT1c,pN0(0/2),cM0,R0,G2
  Ablatio re, LK-Entfernung
  ER>90%, PR<1%, Hercep Test <10%,
  «Luminal B, HER2-neg»
- 01.13 TTE normal
- 02.-05.13 EC x 4
- 06.13 Tamoxifen
  - Dyspnoe – Spiral-Thorax-CT
  - «Tamoxifen hypersensivitätspneumonitis»
  - Stopp Tamoxifen, Steroide
  - Appetitlosigkeit, Dyspnoe, Abgeschlagenheit

• 01.07.13 Spital Davos - ambulant
  Progrediente Symptome
  - CK 68, TnI 0.311 (<0.013), ASAT 122

• 03.07.13 Tachypoe, tachykard, hypoton
  IMC Spital Davos
  aBGA unter 8 l O2
  - pH 7.2, pO2 78, pCO2 15.6 BE -19 Lact 9.1
  - CK 824, TnI 2.32, ASAT 2943
During Rx

Avoid Cardiotoxicity

O.S. 24.10.1952

- Invasiv ductal Breast Cancer
- pT1c (16mm) N0(0/3)(sn)(i-)-cM0
- Breast conserving surgery 08.11
  - ER y1%, PR <1%, Ki-67 30-35%
  - HER-2/neu Score +++
S.R. 19.11.1971

- Invasiv ductal Breast Cancer
- pT2 N0(0/5)(sn)(i-) M0, R0, G3
- Breast conserving surgery 08.11
  - ER y1%, PR <1%, Ki-67 20%, p53-Expression <10%, HER-2/neu 100%, Score ++

LVEF (%) / LVEDD (mm)

Heart Failure

ACE-Inhibitor

Excision

Epi/Endo → Ptx+Trast → Trast
Cardiotoxicity – Prevention/Reduction

Increased risk of cardiac death and heart failure in cancer survivors

Survivor Surveillance

Early treatment prevents cardiac remodeling

Heart failure treatment
**Cardiac Dysfunction / Heart Failure During and After Cancer Therapy**

- **Anthracycline**

- **Risk Factors**
  - Cumulative Dose
  - Combination chemotherapy
  - Prior/concomitant mediastinal radiotherapy
  - Age
  - Previous cardiac disease
  - Hypertension

- **Signaling Inhibitors**

- **Risk Factors**
  - Prior / concomitant anthracyclines
  - Age > 50 y/o
  - Previous cardiac disease
  - Hypertension
  - Higher BMI

Suter, T. M. and M. S. Ewer, Eur Heart J 2013; 34(15): 1102-1111
CARDIOVASCULAR SIDE EFFECTS OF RADIATION THERAPY

Valvular Disease

Cardiac Dysfunction

Ischemia

Conduction Disease

Pericardial Disease
THE HEART – A POSTMITOTIC, COMPLEX ORGAN

Healthy Aortic Valve – Closed

Healthy Aortic Valve – Open

Diseased Aortic Valve – Closed

Diseased Aortic Valve – Open
Cardiotoxicity – Prevention/Reduction

Childhood Cancer Survivors
• signs of cardiotoxicity
• within 10 years after therapy

Survivor

Surveillance

Van der Pal HJ J Clin Oncol. 2012 May 1;30(13):1429-37
Heart Failure Patient

Oncology Patient

Heart Failure Patient

Oncology Patient
ROLE OF CARDIO-ONCOLOGIST

Prior RX
Risk Assessment
- Conventional RF
- Novel RF
- Rx Preexisting Dz

During Rx
Avoid Cardiotoxicity
Manage Side Effects
- Co-Medication
- Early Detection
- Risk Assessment

Survivor
Surveillance
- Early Detection
- Early Treatment
CARDIAC MONITORING OF CANCER PATIENTS DURING CANCER THERAPY

• «normal» LVEF ≥ 55%

• decrease in LVEF of >10 % points, to a value < 50%

• repeat study 3 weeks after baseline study

• LVEF with best method available (ideally 3DE)

• myocardial deformation using 2D speckle-tracking

• combination with biomarkers
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Oncology

Cardiology

Basic Science