Update in Cardio-Oncology

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President of British Cardio-Oncology Society
Chair of HFA Cardio-Oncology Study Group of ESC
Cardiology advisor to Macmillan Cancer
Conflicts of Interest

• Consultancies: Servier, Novartis, AMGEN, Onyx Pharmaceuticals, Ferring Pharmaceuticals, Clinigen Group, BMS

• Research grants: Servier, Pfizer

• Honoraria, speaker fees, conference support: Novartis, Pfizer, Roche, Servier, Astra Zeneca, Bayer, Boehringer Ingelheim

• Advisory boards: Servier, Roche, AMGEN, Onyx Pharmaceuticals, Eli Lily, Clinigen Group, Ferring, Stealth Peptides
Global Cardio-Oncology Summit 2017
September 20-21, 2017
London, UK

Royal Brompton & Harefield
NHS Foundation Trust

Topics include:

• How to deliver a Cardio-Oncology service
• Training in Cardio-Oncology
• eHealth and Cardio-Oncology
• How do I measure the quality of my service?
• Role of primary care in cancer survivors
• Immunotherapy and emerging cardiotoxicity
• Personalised medicine & genetics
• EP session – who should have ablation, ICDs, CRT?
• Anticoagulation and antithrombotic (AF, ACS)
• Radiation-induced cardiotoxicity
• Managing cardiac issues during BMSC transplants
• Hormone therapy and CV risk
• Young Investigator Competition
Cancer Survivorship

- Early detection and improved intervention more people are surviving cancer
- Worldwide cancer survivors within five years of diagnosis estimated 28.7 million for 2008 (WHO)
- 2 million cancer survivors in UK
Overview

- Anthracyclines
- Trastuzumab
- Targeted therapies
- Radiotherapy and HFpEF
- Cardio-Oncology services in the UK

Importance of baseline risk
Real world prevalence
~9% LV dysfunction at 12 months

Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

Daniela Cardinale, MD, PhD, FESC; Alessandro Colombo, MD; Giulia Bacchiani, MD; Ines Tedeschi, MSc; Carlo A. Meroni, MD; Fabrizio Veglia, PhD; Maurizio Civelli, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Giuseppe Curigliano, MD, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

Methods and Results — We assessed left ventricular ejection fraction (LVEF), at baseline, every 3 months during chemotherapy and for the following year, every 6 months over the following 4 years, and yearly afterward in a heterogeneous cohort of 2625 patients receiving anthracycline-containing therapy. In case of cardiotoxicity (LVEF decrease >10 absolute points, and <50%), heart failure therapy was initiated. Recovery from cardiotoxicity was defined as partial (LVEF increase >5 absolute points and >50%) or full (LVEF increase to the baseline value). The median follow-up was 5.2 (quartile 1 to quartile 3, 2.6–8.0) years. The overall incidence of cardiotoxicity was 9% (n=226). The median time elapsed between the end of chemotherapy and cardiotoxicity development was 3.5 (quartile 1 to quartile 3, 3–6) months. In 98% of cases (n=221), cardiotoxicity occurred within the first year. Twenty-five (11%) patients had full recovery, and 160 (71%) patients had partial recovery.

Cardinale et al Circulation 2015 131 1981-88
Doxorubicin Cardiotoxicity

Amplified by:

- Dose
- Age
- Coexisting CV disease
  - Hypertension
  - IHD
  - Diabetes
- DXT effecting cardiac field
- TKIs
- ?Genetic predisposition

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>%</th>
<th>SE</th>
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</thead>
<tbody>
<tr>
<td>50</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>100</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>150</td>
<td>6.5</td>
<td>1.0</td>
</tr>
<tr>
<td>200</td>
<td>7.8</td>
<td>1.2</td>
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<tr>
<td>250</td>
<td>8.8</td>
<td>1.2</td>
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<tr>
<td>300</td>
<td>16.2</td>
<td>1.7</td>
</tr>
<tr>
<td>350</td>
<td>17.9</td>
<td>1.9</td>
</tr>
<tr>
<td>400</td>
<td>32.4</td>
<td>3.2</td>
</tr>
<tr>
<td>450</td>
<td>37.9</td>
<td>3.5</td>
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<tr>
<td>500</td>
<td>53.9</td>
<td>4.2</td>
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<tr>
<td>550</td>
<td>65.4</td>
<td>4.6</td>
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<tr>
<td>600</td>
<td>72.0</td>
<td>4.8</td>
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<tr>
<td>650</td>
<td>80.6</td>
<td>4.9</td>
</tr>
<tr>
<td>700</td>
<td>86.2</td>
<td>4.8</td>
</tr>
<tr>
<td>750</td>
<td>86.2</td>
<td>4.8</td>
</tr>
<tr>
<td>800</td>
<td>90.8</td>
<td>4.9</td>
</tr>
<tr>
<td>850</td>
<td>100.0</td>
<td>—</td>
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</table>

Targeted Molecular Therapies

HER2 targeted therapies
• Trastuzumab
• Pertuzumab
• T-DM1
• Lapatinib

VEGF-Tyrosine Kinase Inhibitors
• Bevacizumab
• Sunitinib
• Sorafenib
• Pazopanib
• Axitinib
• Regorafenib
• Cabozantinib

Raf-MEK pathway inhibitors
• Debrafanib
• Vemurafenib
• Trametinib

BCR-Abl-Tyrosine Kinase Inhibitors
• Imatinib
• Nilotinib
• Dasatanib
• Bosutinib
• Ponatanib

Proteosomal inhibitors
• Bortezomib
• Carfilzomib
• Ixazomib

Immunotherapies
• Nivolumab
• Ipilumimab
• Pembrolizumab
Upregulation of Cardiac HER2 receptors following cardiac injury

De Korte et al European Journal of Cancer 2007 43; 2046 - 2051

111 In-DTPA-trastuzumab SPECT scan in a cancer patient following anthracycline chemotherapy
Cumulative incidence of heart failure in 12,500 women with invasive breast cancer over 5 years by adjuvant chemotherapy group.

The effect of age upon the risk of cardiotoxicity
The effect of age upon the risk of cardiotoxicity
The effect of age upon the risk of cardiotoxicity
Trastuzumab-associated cardiac events in the Persephone trial

Helena M Earl¹,²,³, Anne-Laure Vallier⁴, Janet Dunn⁵, Shrushma Loi⁵, Emma Ogburn⁵, Karen McAdam⁶, Luke Hughes-Davies¹,³, Adrian Harnett⁷,⁸, Jean Abraham¹,²,³, Andrew Wardley⁹, David A Cameron¹⁰, David Miles¹¹, Ioannis Gounaris¹²,¹³, Chris Plummer¹⁴ and Louise Hiller⁵

- Prospective RCT comparing 6m and 12m adjuvant Trastuzumab for HER2+ early stage breast cancer
- 2500 patients 22-82 years
- 93% received ACs, 49% AC+taxanes
PERSEPHONE Trial

- 3 cardiac deaths in 12m and 1 cardiac death in 6m
- Clinical cardiac dysfunction more common in 12m arm
  - 9% in 6m arm
  - 12% in 12m arm
- Cardiotoxicity most common reason for interrupting Herceptin
  - 4% in 6m arm
  - 6% in 12m arm
- Risk factors
  - Low baseline LVEF (<55%)
  - >3 cycles of AC
  - Age (OR 2.72 for 70+yrs vs <50yrs)
  - Prior use of cardiac medication

Earl H et al BRC 2016 115 1462-70
Trastuzumab duration and LV dysfunction
Dose-duration related

Frequency of LVSD

- **PHARE Trial**¹ (3380pts)
  - 6m 3%
  - 12m 6%
- **PERSEPHONE Trial**² (2500pts, median age 55yrs)
  - 6m 9%
  - 12m 12%
- **HERA Trial**³ (5102pts, median age 49yrs)
  - 12m 4%
  - 24m 7%

1. Pivot et al Eur J Cancer 2015 51 1660-1666
2. Earl et al BRC 2016 115 1462-70
Cardiac biomarkers and risk of trastuzumab-induced cardiotoxicity (TIC)

- HERA trial adjuvant trastuzumab for HER2+ breast cancer (>5000 patients)
- 533 patient cardiotoxicity substudy
- Baseline pre Trastuzumab (Herceptin)
- Elevated baseline troponin in 19% patients
- Predicted increased risk of TIC (HR 3.57-4.52)
- During Trastuzumab (Herceptin)
- Rare troponin rises during treatment
- Trend for increasing NT-proBNP during treatment to predict LVEF reduction

Zardavas et al JCO 2017 35 878-884
Impact of interrupting Herceptinin upon cancer recurrence

Memorial Sloane Kettering, New York
546 HER2+ve Breast Cancer Patients – Adjuvant tx

<table>
<thead>
<tr>
<th>Characteristics of patients with and without breast cancer recurrence¹</th>
<th>No Breast Cancer Recurrence (n=491)</th>
<th>Breast Cancer Recurrence (n=55)</th>
<th>p value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>50.9 ± 0.5</td>
<td>52.8 ± 1.8</td>
<td>0.090</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 ± 0.3</td>
<td>26.4 ± 0.8</td>
<td>0.529</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>2.2 ± 0.1</td>
<td>2.0 ± 0.2</td>
<td>0.154</td>
</tr>
<tr>
<td>Histologically positive nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>232 (47.3)</td>
<td>21 (38.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-3</td>
<td>177 (36.0)</td>
<td>13 (23.6)</td>
<td></td>
</tr>
<tr>
<td>≥ 4</td>
<td>82 (16.7)</td>
<td>21 (38.2)</td>
<td></td>
</tr>
<tr>
<td>Progesterone-receptor status positive</td>
<td>260 (53.0)</td>
<td>18 (32.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Estrogen-receptor status positive</td>
<td>320 (65.2)</td>
<td>31 (56.3)</td>
<td>0.228</td>
</tr>
<tr>
<td>Trastuzumab Interruption &gt; 1 cycle, all causes (excluding disease progression)</td>
<td>62 (12.6)</td>
<td>14 (25.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Trastuzumab Interruption &gt; 1 cycle, due to Trastuzumab Cardiotoxicity</td>
<td>45 (9.1)</td>
<td>9 (16.4)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

¹Values are mean ± standard error of mean (SEM) for continuous variables and N (%) for categorical variables.
²p-value represents difference in time to breast cancer recurrence. p-value from the Cox proportional model for continuous variables and the log rank test for categorical variables.

Yu AF et al Breast Cancer Res Treat. 2015 Jan;149(2):489-95
Cardiovascular toxicity of other cancer therapies
Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

Supplementary Table S7. Summary of Patients With On-Therapy Left Ventricular Ejection Fraction Dysfunction Symptoms of Cardiac Dysfunction (Safety Population)

<table>
<thead>
<tr>
<th>Patients meeting one or more cardiac dysfunction criteria</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pazopanib N = 554</td>
</tr>
<tr>
<td>Patients meeting one or more cardiac dysfunction criteria</td>
<td>47 (13)</td>
</tr>
<tr>
<td>Criterion 1. Symptoms of cardiac dysfunction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Criterion 2. ≥15% absolute decline in LVEF compared to baseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32 (9)</td>
</tr>
<tr>
<td>Criterion 3. ≥10% absolute decline in LVEF compared to baseline and below LLN&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24 (7)</td>
</tr>
</tbody>
</table>

Abbreviations: LLN, lower limit of normal range; LVEF, left ventricular ejection fraction.

<sup>a</sup>Percentages are based on 362 pazopanib patients and 369 sunitinib patients with post-baseline LVEF assessment or symptoms of cardiac dysfunction.
Cardiovascular risk with proteasomal inhibitors for multiple myeloma
Cardiovascular SAEs in RCTs
Phase 3 Carfilzomib Trials

• ASPIRE Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Carfilzomib Group (N=392)</th>
<th>Control Group (N=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 or Higher</td>
</tr>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>76 (19.4)</td>
<td>11 (2.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56 (14.3)</td>
<td>17 (4.3)</td>
</tr>
<tr>
<td>Acute renal failure†</td>
<td>33 (8.4)</td>
<td>13 (3.3)</td>
</tr>
<tr>
<td>Cardiac failure‡</td>
<td>25 (6.4)</td>
<td>15 (3.8)</td>
</tr>
<tr>
<td>Ischemic heart disease§</td>
<td>23 (5.9)</td>
<td>13 (3.3)</td>
</tr>
</tbody>
</table>

Total Cardiac AEs

26.6% 11.4% 15.6% 5.7%

Total Cardiac AEs + Dyspnoea

46% 14.2% 30.5% 7.5%

DVT/PE

10.2% 6.2%

Stewart et al N Engl J Med. 2015 Jan 8;372(2):142-52
Immunotherapy and myocarditis

- Emerging problem
- Immune-mediated myocarditis
- Incidence not clear
  - Initially considered rare
  - More attention, more cases
  - Associated with generalised myositis
- Severe cases
  - Fulminant myocarditis
  - Heart block
  - VT/VF, SCD
- Risk factor profile not understood
  - Pre-existing CVD
  - Pre-existing autoimmune disease
  - Cardiac antigen expression in tumour

Johnson DB et al NEJM 2016 375 1749-55
Cancer drugs and arrhythmias

Ibrutinib (Imbruvica): reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and of opportunistic infections

From: Medicines and Healthcare products Regulatory Agency
Published: 15 August 2017
Therapeutic area: Cancer, Cardiovascular disease and lipidology, GI, hepatology and pancreatic disorders, Haematology, and Infectious disease
Risk of Heart Failure with preserved EF (HFpEF) in women after contemporary breast cancer radiotherapy

• Population-based case-control study from Olmstead County
  – 945 breast cancer patients who received DXT (1998-2013)
  – Mean interval from radiotherapy to HF was 5.8±3.4 years.
• 70 HF cases (59 used in study)
  – 64% had LVEF >50%
• 111 matched controls
  – Age, DM, ↑BP, tumour side, chemotherapy

Saiki H et al Circulation 2017 135 1388-1396
Frequency of heart failure (HF) according to mean cardiac radiation dose (MCRD)

Saiki H et al Circulation 2017 135 1388-1396
Frequency of heart failure according to mean cardiac radiation dose (MCRD)
Effect of risk factors before breast cancer diagnosis

Saiki H et al Circulation 2017 135 1388-1396
2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Authors/Task Force Members: Jose Luis Zamorano* (Chairperson) (Spain), Patrizio Lancellotti* (Co-Chairperson) (Belgium), Daniel Rodriguez Muñoz (Spain), Victor Aboyans (France), Riccardo Asteggiano (Italy), Maurizio Galderisi (Italy), Gilbert Habib (France), Daniel J. Lenihan¹ (USA), Gregory Y. H. Lip (UK), Alexander R. Lyon (UK), Teresa Lopez Fernandez (Spain), Dania Mohty (France), Massimo F. Piepoli (Italy), Juan Tamargo (Spain), Adam Torbicki (Poland), and Thomas M. Suter (Switzerland)
ESC Position statement on Cardio-Oncology

9 pillars of Cardio-Oncology

- Myocardial dysfunction and heart failure
- Coronary artery disease
- Valvular heart disease
- Arrhythmias and QT
- Arterial hypertension
- Thromboembolic disease
- Peripheral vascular disease and stroke
- Pulmonary hypertension
- Pericardial complications

Zamarano et al EHJ 2016 37 2768-2801
Baseline Risk Assessment

• Previous cardiovascular disease
  – HF, IHD, Borderline LVEF, LVH, Elevated cardiac biomarkers

• Demographic and other CV risk factors
  – Age, hypertension, diabetes, renal failure

• Previous cardiotoxic cancer treatment
  – ACs, DXT, previous Herceptin-induced LVSD

• Lifestyle risk factors
  – Obesity, Smoking
Surveillance in Cancer Survivors

• Late symptoms
  – Fatigue, dyspnoea, chest pain, palpitations
  – New HF presentations – ask about cancer history

• Collaboration approach between primary care, cardiology and oncology

THINK HEART
The Cardio-Oncology Team

- Cardiologist
- Oncologist
- Palliative Care
- CMR Physician
- Echo cardiographer
- Cardio-Oncology Nurse
- Cardio-Oncology Fellow
Cardio-Oncology
National and International Impact

British Cardiovascular Society
Cardio-Oncology Services in the UK

British Cardio-Oncology Society

The British Cardio-Oncology Society (www.bco-os.org) was formed in 2012 by a group of UK cardiologists and oncologists from multiple specialities interested in and working on the cardiovascular effects of cancer treatment. Our mission is to promote research, best clinical practice and a wider understanding of the effects of cancer treatment on the cardiovascular system. The society is an associated professional group of the British Cardiovascular Society (www.bcsvs.org) which we hold a dedicated cardio-oncology session at the Annual Scientific Meeting in Manchester on 9th June 2015. We work with local, national and international partners to improve patient care and welcome enquiries from cardiologists, oncologists, clinicians, the NHS and industry.

More information will be available here soon. For further information about the society, contact info@bco-os.org.

www.bc-os.org