Managing LV Impairment with Cancer Therapies

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Conflicts of Interest:  St Jude Medical, Servier, Pfizer, Novartis, Bristol Myers Squibb, Astra Zeneca
Cancer Treatment: improved survival

- Risk factors
- Surgery
- Radiotherapy
- Chemotherapy

Cancer survivors
- Cancer therapies: cardiac complications
- Cardiovascular risk = recurrence risk

Cardio-oncology collaboration

Data from Cancer UK
## Chemotherapy: conventional agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency of Use</th>
<th>Cardiac Cx Rate</th>
<th>Cardiac Complications</th>
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<tbody>
<tr>
<td><strong>Anthracyclines</strong></td>
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</table>
| doxorubicin (adriamycin), daunorubicin, epirubicin | +++ | +++ | HF/LV dysfunction  
• Cumulative dose-dependent  
• Young/Old, ♀, DXT, IVI, cardiac RFs  
• liposomal delivery, dexrazoxane |
| **Alkylating Agents** | | | |
| Busulfan | + | + | Endomyocardial fibrosis, tamponade |
| Cisplatin | +++ | ++ | Cardiac ischaemia, HT, HF |
| Cyclophosphamide | +++ | + | Haemorrhagic pericarditis (high dose)  
HF: cumulative-dose, anthracyclines, elderly, DXT |
| **Anti-Metabolites** | | | |
| 5-Fluorouracil | +++ | ++ | Cardiac ischaemia: DXT, cisplatin, rate/dose-dependent |
| **Anti-microtubules** | | | |
| Paclitaxel | +++ | + | Heart block, VT, HF |
| Vinca alkaloids | ++ | ++ | Cardiac ischaemia |

adapted from Circulation 2004;109:3122
Living organisms or substances derived from living organisms, or laboratory-produced versions of such substances used to treat disease:

**Immunotherapy:** stimulate host immune response to act directly against cancer cells

**Targeted therapy:** interfere with signalling processes to affect tumour growth

- **Monoclonal antibodies:**
  - Rituximab: CD20 antigen on B-cell non-Hodgkin lymphoma
  - Trastuzumab: Human Epidermal Growth Factor-2 (HER-2) in breast cancer

- **Cytokines**
  - Intron A (interferon-α): Kaposi’s sarcoma, haematological cancers
  - Aldeleukin (interleukin-2): metastatic renal cell cancer, melanoma

- **Treatment vaccines**
  - Provenge (sipuleucel-T): boosts host immune system in prostate cancer

- **Oncolytic viruses**
  - OncoVex (herpes virus): infects and kills cancer cells (inoperable melanoma)
Anthracyclines: spectrum of use

Data from UK Cancer Registry

Anthracyclines: used in >50% of solid organ tumours and haematological malignancies

Derived from *Streptomyces Peucetius*
1\textsuperscript{st} compound: *Daunorubicin*
14-hydroxy version: *Doxoryubicin (adriamycin)*
Others: *Epirubicin, Idarubicin, Pirarubicin*

Learn the terminology
- Lymphoma: CHOP, R-CHOP
- Breast cancer: AC, FEC, CMF
Anthracyclines: mode of action

Oxidative Stress Hypothesis

- Anthracyclines
  - Iron
  - Mitochondrial respiration

- Antioxidants
  - ODIF
  - ODIF scavengers

- Lipid, protein, DNA damage
- Cell dysfunction/death

Heart Metab 2007;35:1

myocardial biopsy

A. myofibrillar drop out
B. necrosis apoptosis
C. mitochondrial vacuolation
D. sarcoplasmic reticulum swelling
Anthracyclines: natural history

Long-term follow-up meta analysis (n=137 studies)

Acute (<24hrs): <1%
Arrhythmias, myopericarditis, rarely acute HF

Early (24hrs-1year): 10%
Mainly asymptomatic mild LVSD

Late (>1year): 30-40%
~1/3 mild, 1/3 moderate, and 1/3 severe LVSD

“the cured cancer survivor of today is at risk of becoming the heart failure patient of tomorrow” Position Statement: Heart Failure Association of the European Society of Cardiology

cardio-oncology collaboration and long-term patient follow-up important
Cancer Survivors: pre-clinical disease

Cardiff Cardio-Oncology collaboration:

• Can we identify pre-clinical disease in cured cancer patients receiving high-dose anthracyclines with preserved LV systolic function through exercise stress echo?

LV Mechanics

Ventriculo-Arterial coupling @ rest and exercise

Arterial Pulse Wave

patient consent obtained
Cancer Survivors: pre-clinical disease

Cardiff Cardio-Oncology Collaboration:

- 13 long-term cancer survivors: age 36±10yrs, 11±8yrs post treatment
- HL (23%), NHL (46%), Ewing’s sarcoma (8%), ALL (23%)
- All received Doxorubicin: 317mg/m², 62% received radiotherapy
- Incremental sub-maximal exercise stress echo
- Responses compared with 13 age-matched healthy controls

“despite normal resting measures of global systolic cardiac function, long-term cancer survivors demonstrate significantly blunted markers of cardiac deformation during physiological stress echo”
Anthracyclines: cumulative dose & chelation

Risk of LVSD and cumulative dose

Co-administration of iron chelator (Dexrazone)
- Cochrane review
- Meta-analysis of cardiac events ± dexrazone

But: ↑ risk of 2nd malignancy

Bull du Cancer 2004;91:s3,185

J Clin Oncol 2007;25:493
Anthracyclines: monitoring

**Imaging**

**CTRCD:** ↓ of EF >10% points to a value below normal

*Imaging techniques are not interchangeable*

**MUGA:**
- Radiation, reproducible, EF value only

**Echo:**
- Systolic, diastolic, & valve function
- Right heart, PA pressure
- Sub-clinical disease

**Cardiac MRI:**
- Systolic, diastolic, & valve function
- Scar tissue

**Troponin:** marker of cardiac necrosis

![Graph showing LVEF reduction (%)](Circulation 2004;109:2749)

**Natriuretic peptides:** marker of LVEDP

![Graph showing change in biomarkers](Eur J Heart Fail 2005;7:87)
**Anthracyclines: ACE-inhibitors**

**Troponin targeted ACE-I therapy**

473pts: high dose chemotherapy

Mainly lymphomas + anthracycline

Randomised at 1 month:

- **enalapril** (10mg/day)
- **placebo**

Serial echos: I° EP change in EF

Analysis with respect to troponin

*Circ 2006;114:2474*
Un-guided beta blockers: randomised study

50pts: anthracycline treatment
Randomised at induction: carvedilol (12.5mg/day) v no treatment
Serial echos: I° EP change in EF
**Trastuzumab**: Herceptin

**Breast cancer and Herceptin**

- ~20% of breast cancers: HER-2 positive
- Herceptin: monoclonal Ab to HER-2
- Adjuvant Rx: 4-6 weeks post chemotherapy
- IV infusion every 3 weeks for 1 yr
  - 30% ↓ breast cancer mortality
  - 50% ↓ cancer relapse

**Erb B2 knockout mice**

*Nature 2002;8:459*  
*New Eng J Med 2005;353:1659*
Trastuzumab: cardiac toxicity

Cardiotoxicity risk profile

- NOT free-radical mediated
- NO structural myocyte damage
- HER-2 signalling pathways mediating normal cell growth, repair, and survival
- Dose independent
- Early onset (<6 weeks of treatment)
- 6-fold ↑ when used after initial anthracycline chemotherapy
- More likely in older patients with EF at lower limit of normal at baseline

Myocardial Dysfunction is REVERSIBLE

Single Centre Experience

- 4yr period: 38pts referred (~950 treated: 4%)
- HER-2+ve breast cancer treated with anthracyclines, followed by Trastuzumab
- LVSD: >10% drop in EF and below LLN

- Reversible LV dysfunction in >97% of patients
- Trastuzumab re-challenge: 88% EF preserved

J Clin Oncol 2005;23:7820
1.1 Trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

1.2 Cardiac function should be assessed prior to the commencement of therapy and trastuzumab treatment should not be offered to women who have a left ventricular ejection fraction (LVEF) of 55% or less, or who have any of the following:

- a history of documented congestive heart failure
- high-risk uncontrolled arrhythmias
- angina pectoris requiring medication
- clinically significant valvular disease
- evidence of transmural infarction on electrocardiograph (ECG)
- poorly controlled hypertension.

1.3 Cardiac functional assessments should be repeated every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to below 50% then trastuzumab treatment should be suspended. A decision to resume trastuzumab therapy should be based on a further cardiac assessment and a fully informed discussion of the risks and benefits between the individual patient and their clinician.
SUMMARY: cardiac implications of chemotherapy

Major advances in oncology treatments:
• Survival doubled in last 50 years
• Many therapies → cardio-toxicity
• Conventional HF treatments: improve cardiac function
• Avoid the cured cancer patient of today becoming the HF patient of tomorrow

Cardio-Oncology Collaborations
• Bi-directional learning: specific cardio-toxic profiles
• Identification of high risk patients and patients with early complications
• Biomarkers: emerging evidence, not currently mandated
• Care pathways and rapid access to specialist clinics
• LVSD patient: conventional neurohormonal HF treatments ± device therapy
• Cancer recurrence + LVSD patient: complex multi-disciplinary decisions
• Long-term surveillance: Cardiac risk factor management and late LVSD
questions?

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