Chemotherapy-Related Cardiac Dysfunction

& How a Cardiology-Oncology Clinic Can Help!

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Chemotherapy-Related Cardiac Dysfunction

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>LVEF</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At high risk for HF</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>B1</td>
<td>Occult LV dysfunction</td>
<td>LVEF &gt; 53%, abnormal strain and/or cardiac biomarkers</td>
<td>No</td>
</tr>
<tr>
<td>B2</td>
<td>Overt LV dysfunction</td>
<td>LVEF &lt; 53%</td>
<td>No</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic HF, responsive to conventional therapy</td>
<td>LVEF &lt; 53%</td>
<td>Yes</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic HF, unresponsive to conventional therapy</td>
<td>LVEF &lt; 53% (usually lower)</td>
<td>Persistent NYHA IV</td>
</tr>
</tbody>
</table>

Key Learning Objectives

• To provide a brief background about cardio-oncology
• To define chemotherapy-related cardiac dysfunction and review the incidence, mechanism and risks associated with various agents
• To highlight an approach to care and patient risk assessment
• To review the Canadian Cardiovascular Society Guidelines for the Evaluation and Management of Cardiovascular Complications of Cancer Therapy and select clinical trials including: strategies for prevention, detection & surveillance and treatment of chemotherapy-related cardiac dysfunction
• To share the South Health Campus (SHC) Cardio-Oncology Clinic service model
• To discuss implications for pharmacists and patients

Cardio-Oncology

• Emerging subspecialty that aims to “optimize cardiac care for cancer patients”
• Increasing rates of both cancer survival and morbidity & mortality from cardiovascular causes
• Shared population & risk factors
• Cardiovascular health linked to improved cancer outcomes
• Multidisciplinary collaboration
• “Cure Cancer, Save Hearts”

Chemotherapy-Related Cardiac Dysfunction

- Anthracyclines
  - Mechanism:
    - Impaired protein synthesis & production of reactive oxygen species
    - Bind to DNA and topoisomerase II-beta in cardiac myocytes → myocytol injury & cell death
  - Early (1.6 ~ 2.1%)
    - Within first year of treatment
    - Can be asymptomatic, continuous, progressive decline in LVEF
    - Usually reversible → good functional recovery if detected and treated early with HF medications
  - Late (1.6 ~ 5%)
    - After first year of treatment
    - Decline LVEF followed by clinical decompensation
    - Usually irreversible

- Other agents
  - Imatinib
  - Tyrosine kinase inhibitors
  - Bevacizumab
  - Peptides
  - Denosumab
  - Other drugs

- Late presentations
  - Persistent LV dysfunction
  - Amyloidosis
  - Glycogen storage disease

- Management
  - Monitoring
  - Prophylactic drugs
  - Cardiac monitoring
  - Early intervention

Cancer Treatment

Cancer Status

Support Services

Community

Cardiology Team

CJC 2016; 831:941
E002661 Canadian Cardio-Oncology Network (CCON) http://cardiooncology.ca
**HER2-Inhibitors**

- **Features:**
  - Usually appears during treatment
  - Generally not dose related
  - Likely reversible
  - Concomitant or previous use of anthracyclines or paclitaxel increases risk

**Other Agents**

- **VEGF Inhibitors**
  - Incidence: bevacizumab (1.6-4%), sunitinib (2.7-19%), sorafenib (4-8%), dacarbazine (2.4-6%), imatinib (0.2-7.6%)
  - Mechanism: inhibition of vascular endothelial growth factor receptor-mediated angiogenesis → mitochondrial damage
  - Features: generally reversible

**Approach to Care**

1. Identify patients at increased risk of developing chemotherapy-related cardiac dysfunction
2. Optimize management of cardiovascular risk factors and comorbidities
3. Monitor patients while receiving chemotherapy
4. Monitor patients after completion of chemotherapy (surveillance)
5. Manage patients that experience chemotherapy-related cardiac dysfunction with medications and lifestyle recommendations

**Risk Assessment**

**Cardiac Factors:**
- Heart failure
- Left ventricular dysfunction
- Coronary artery disease
- Moderate or severe valvular heart disease
- Arrhythmias
- Cardiomyopathy
- Cardiac sarcoidosis involving myocardium

**Cancer Treatment Factors:**
- High cumulative dose of anthracycline
- Timing of administration of anthracycline and other chemotherapy agents
- Prior anthracycline use
- Prior or current radiation therapy involving the heart
- Curative vs palliative intent

**CCS Guidelines: Risk Assessment**

“We recommend evaluation of traditional cardiovascular risk factors and optimal treatment of cardiovascular disease, as per current CCS guidelines, be part of routine care for all patients before, during, and after receiving cancer therapy
(Strong Recommendation, Moderate-Quality Evidence).

We recommend that patients who receive potentially cardiotoxic cancer therapy undergo evaluation of LV ejection fraction (LVEF) before initiation of cancer treatments known to cause impairment in LV function
(Weak Recommendation, Moderate-Quality Evidence).”

**Prevention**

- **Cardioprotective medications**
  - ACE/ARB
  - BB
  - Statins

- **Treat risk factors and comorbidities**
- **Positive health-promoting behaviour**
- **Cancer treatment considerations**
  - Less cardiotoxic agents
  - Limit anthracycline cumulative doses
  - Administration technique & formulation
  - Minimize cardiac irradiation
**PRADA**

**RCT, FC, DB, 2 x 2 factorial, ITT, single center in Norway**

**P**
Adult women with early breast cancer receiving adjuvant chemotherapy with 5-fluorouracil, epirubicin and cyclophosphamide (FEC)

LVEF > 50%

No prior cardiac disease

~22% received trastuzumab and ~30% taxanes after FEC

I
- Candesartan 32 mg daily + metoprolol succinate 100 mg daily (n=31)
- Metoprolol succinate + placebo (n=31)

C
- Placebo + placebo (n=33)

Initiated prior to chemotherapy & continued 10 – 61 weeks during adjuvant treatment period

**O**
Change in LVEF from baseline to completion of adjuvant therapy by CMR:

- 0.5% candesartan + metoprolol (P = 0.035 compared to placebo-placebo)
- 0.5% candesartan + placebo (P = 0.025 compared to placebo-placebo)
- 2.5% metoprolol + placebo (P = 0.71 compared to placebo-placebo)
- 2.4% placebo + placebo (control)

Secondary = No symptomatic HF

No significant change in RVCL, LV diastolic function, troponin or BNP levels

**MANTICORE 101-Breast**

**RCT, PC, DB, ITT, 2 centers in Canada**

**P**
Adult women with HER2 positive early breast cancer receiving adjuvant trastuzumab therapy

- 87.8% doxorubicin, carboplatin and trastuzumab (TCH)
- 12.5%-5 FU, epirubicin and cyclophosphamide followed by doxorubicin and trastuzumab (FEC- DH)

LVEF > 50%

No prior cardiac disease

I
- Perindopril 8 mg (n=32) or bisoprolol 10 mg (n=31)

Initiated within 7 days of trastuzumab & continued during adjuvant period (usually 12 months)

C
- Placebo (n=33)

**D**
Primary = change in indexed LV end diastolic volume (LVEDV in ml/m2) from baseline to completion of trastuzumab therapy:

- T perindopril + 8 bisoprolol and + placebo (P = 0.32)

Secondary = change in LVEF from baseline to completion of trastuzumab therapy by CMR:

- 2% bisoprolol vs -2% placebo (P = 0.001)

CTBCD > 10% percentage decline in LVEF to <50%:

- 1% perindopril vs 3% bisoprolol placebo (P = 0.03 post-cycle 4) (95% post-cycle 17)

Clinical cardiotoxicity = 7 day interruption in trastuzumab due to LV dysfunction

9% perindopril vs 9.7% bisoprolol vs 3% placebo (P = 0.03)

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**Atorvastatin**

**Evidence for Prevention**

**Strengths:**

- RCT data
- Low to moderate doses of anthracyclines
- With or without trastuzumab
- Endpoints with imaging data from CMR
- Primary prevention of LVEF decline may reduce long-term risk of cardiac dysfunction

**Limitations:**

- Small sample sizes
- Heterogeneity
- Low cardiac risk
- Variation in combination and duration of cardioprotective medication regimens
- Different surrogate primary endpoints
- Extent of clinical benefit?
- Exposure to potential side effects & drug interactions
- Cost

**CCS Guidelines: Prevention**

“We suggest that in patients deemed to be at high risk for cancer treatment-related LV dysfunction, an ACE inhibitor or angiotensin receptor blocker, and/or a beta-blocker, and/or statin be considered to reduce the risk of cardiotoxicity.”

**Weak Recommendation**

**Moderate-Quality Evidence**

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**Detection & Surveillance**

**Bottom line**

Individualized monitoring strategy tailored based on risk assessment, signs & symptoms of HF & results of cardiac imaging and biomarkers
Treatment

- Prompt treatment
- Risk vs benefit assessment
- Cancer treatment considerations
  - Holding medications
  - Dose reductions
  - Switching to less cardiotoxic agents

Heart failure therapy
- ACEI/ARB
- BB
- MRA
- Diuretics/symptom management

Enalapril or Enalapril + Beta-Blocker

- Prospective, single centre in Milan between June 1, 1995 and May 31, 2004

P
- Adult patients (n=2625)
  - Mainly non-Hodgkin lymphoma and breast cancer receiving anthracyclines
  - LVEF ≥ 50% or HF symptoms and excluded other causes for cardiac dysfunction

I
- Enalapril (5 mg/day) or enalapril + carvedilol
  - Initiated within 4 months (median) and up-titrated to maximum tolerated doses
  - Follow up: ECHO at baseline, q3mo or lvef > 13%
  - q3mo for the first 2 following years then q6mo until the end of study (median follow up = 3 years)

O
- Primary = LVEF response to HF therapy
  1. 42% (n=108) full response (LVEF ≥ 50%) – 12% NYHA III or IV LVEF 41% prior to HF treatment, 70% on ACEI & BB, HF treatment initiated within 2 months, complete reversal within 7 months
  2. 13% (n=36) partial response (LVEF increased > 10 points but remained < 50%)
  3. 45% (n=90) non-responders (LVEF increased < 10 and remained < 50%)

Enalapril or Enalapril + Carvedilol

- Prospective, single centre in Milan between March 1, 2000 and March 1, 2008

P
- Adult patients who received anthracyclines (n=201) mostly de novo H&N cancer & sarcoma
  - LVEF ≥ 45% +/- HF symptoms and excluded other causes for cardiac dysfunction

I
- Enalapril (5 mg/day) or enalapril + carvedilol
  - Initiated within 4 months (median) and up-titrated to maximum tolerated doses
  - Follow up: ECHO at baseline, q3mo or lvef > 13%
  - q3mo for the first 2 following years then q6mo until the end of study (median follow up = 3 years)

O
- Primary = LVEF response to HF therapy
  1. 48% (n=98) full response (LVEF ≥ 50%) – 12% NYHA III or IV LVEF 41% prior to HF treatment, 70% on ACEI & BB, HF treatment initiated within 2 months, complete reversal within 7 months
  2. 13% (n=26) partial response (LVEF increased > 10 points but remained < 50%)
  3. 45% (n=90) non-responders (LVEF increased < 10 and remained < 50%)

Enalapril or Enalapril + Beta-Blocker

- Prospective, single centre in Milan between June 1, 1995 and May 31, 2004

P
- Adult patients (n=2625)
  - Mainly non-Hodgkin lymphoma and breast cancer receiving anthracyclines
  - LVEF ≥ 50% or HF symptoms and excluded other causes for cardiac dysfunction

I
- Enalapril (before 1999) or enalapril + carvedilol (beep/stop) (after 1999)
  - Initiated promptly upon detection, up-titrated to max tolerated doses
  - Follow up: ECHO at baseline, q3mo or lvef > 13%
  - q3mo during the following 4 years then annually (median follow up = 5.2 years)

O
- Primary = time of occurrence of cardiotoxicity  reduction in LVEF > 10 points from baseline and < 50% by ECHO:
  - 9% (n=226) developed cardiotoxicity (dose-dependent)
  - Median time = 3.5 months after last dose of anthracycline (26% within the first year)
  - 82% (n=180) recovered from cardiotoxicity after the initiation of HF treatment
  - 11% (n=25) fully recovered (LVEF increase to the baseline)
  - 18% (n=42) did not recover and were more likely to be in NYHA III-IV less tolerant to cardiac medications, lower LVEF before HF therapy and had a higher incidence of adverse cardiac events
**Evidence for Treatment**

**Strengths:**
- Prospective trials
- Heart failure evidence-based ACEI and beta blockers
- Early detection and prompt treatment may result in recovery of heart function

**Limitations:**
- Blinded RCTs lacking
- Various definitions of cardiac dysfunction & response to therapy
- Heterogeneity
- Mainly patients with anthracycline-related cardiac dysfunction
- Approach not independently validated
- Ideal cardiac medication treatment regimen and initiation of therapy?
- Optimal duration of therapy?

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**CCS Guidelines: Treatment**

“We recommend that in cancer patients who develop clinical HF or an asymptomatic decline in LVEF (eg, > 10% decrease in LVEF from baseline or LVEF < 53%) during or after treatment, investigations, and management follow current CCS guidelines. Other causes of LV dysfunction should be excluded (Strong Recommendation, High-Quality Evidence).

We suggest that patients at high risk of cancer therapy-related cardiovascular disease or patients who develop cardiovascular complications during cancer therapy (eg, > 10% decrease in LVEF from baseline or LVEF < 53%) be referred to a cardio-oncology clinic or practitioner skilled in the management of this patient population, for optimization of cardiac function and consideration of primary or secondary prevention strategies (Suggestion, Low-Quality Evidence).”

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**Implications for Pharmacists**

1. Who do we treat?
2. How do we treat them?
3. What is most important to the patient?
4. Research & evidence is growing
5. Care is evolving

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