How to Mitigate Cardiotoxicity: Statins and Proton Therapy for All Childhood and Adult Cancer Patients and Survivors?

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• Ehrhardt
  – Nothing to disclose

• Hundley
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  – Stockholder: Prova, Inc.
Outline

- Epidemiology of CV disease related to XRT
- Mechanisms of CV disease after XRT
- Risk factors associated with XRT and CVD
- Review of techniques/research to mitigate XRT associated CVD
- Suggested management and unanswered questions related to XRT associated CVD
Early suggestion of XRT associated CV disease

- 7941 individuals randomized to receive post-mastectomy XRT before 1975.
- Excess CV events after: cobalt source, left breast area XRT.

Latent, dose dependent occurrence of XRT related CVD

- Nested case-control study of 325 Hodgkin lymphoma survivors (Aged 26 to 50 years, Rxed from 1965-1995) compared to 1204 matched controls.
- CHD (myocardial infarction or angina requiring intervention)

CVD associated with radiation treatment

- Pericarditis
- Pericardial fibrosis
- Diffuse myocardial fibrosis
- Coronary artery disease
- Myocardial ischemia
- Valvular heart disease
- Conduction disease
- Heart innervation injury
- Implantable device issues

Differences in coronary artery disease patterns after XRT

<table>
<thead>
<tr>
<th>Lesion characteristics</th>
<th>Radiogenic coronaryitis</th>
<th>Typical CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent anatomical site</td>
<td>Main ostia</td>
<td>Branching sites</td>
</tr>
<tr>
<td>Wall orientation</td>
<td>Concentric since the beginning</td>
<td>Initially eccentric</td>
</tr>
<tr>
<td>Onset time</td>
<td>Younger age (&lt;50 years)</td>
<td>Elder age (&gt;50 years)</td>
</tr>
<tr>
<td>Fibrous component</td>
<td>Prevalent</td>
<td>Variable</td>
</tr>
<tr>
<td>Lipid component</td>
<td>Less represented</td>
<td>Typically present</td>
</tr>
<tr>
<td>Length extension</td>
<td>Longer</td>
<td>Focal</td>
</tr>
<tr>
<td>Treatment of choice</td>
<td>PTCA or CABG</td>
<td>PTCA &gt; CABG</td>
</tr>
</tbody>
</table>

Potential mechanisms of myocardial ischemia after XRT

Macrovascular injury accelerates age-related atherosclerosis, leading to coronary artery disease (years/decades post-RT)

↓

Reduced flow to a “territory” of myocardium

Microvascular injury reduces capillary density (within months of RT)

↓

Reduced collateral flow/vascular reserve (often subclinical)

Combine to cause myocardial ischemia

Fig. 4. An outline of how microvascular and macrovascular radiation-related cardiac injury could theoretically combine to cause myocardial ischemia after RT.

Valvular heart disease after XRT

- 40% to 43% experience valve thickening
- 3% to 17% experience valve dysfunction

RT and heart disease in childhood cancer survivors

RT and heart disease in adult cancer survivors

Major Coronary Event

Any Cardiovascular Event


CVRFs potentiate RT-associated HF

- Evaluate relative contribution of CV risk factors towards heart failure
  - Longitudinal evaluation
  - 10,724 survivors, CCSS
  - Is risk simply additive?
  - Hypertension potentiates radiation-associated risk for heart failure
  - Multiple traditional CV risk factors increase risk

Cumulative Risk of at Least One Acute Coronary Event (%)

- Radiotherapy with mean heart dose of 10 Gy
- Radiotherapy with mean heart dose of 3 Gy
- No radiotherapy

Cumulative Risk of Death from Ischemic Heart Disease (%)

- Radiotherapy with mean heart dose of 10 Gy
- Radiotherapy with mean heart dose of 3 Gy
- No radiotherapy

Risk factors for CV disease after receipt of XRT

Table 1 Radiation-induced heart disease depends on other factors related to whole cancer therapy, patients’ characteristics and clinical history

<table>
<thead>
<tr>
<th>Additional risk factors for radiotherapy cardiovascular disease</th>
</tr>
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<tbody>
<tr>
<td>Total dose &gt;30 Gy or fractioned dose &gt;2 Gy/day [4, 7]</td>
</tr>
<tr>
<td>Heart volume exposed [4, 7, 17]</td>
</tr>
<tr>
<td>Time since exposure [19–21, 41]</td>
</tr>
<tr>
<td>Adjunctive chemo/hormone therapy [101, 111–115]</td>
</tr>
<tr>
<td>Presence of general risk factors [38, 54, 75, 76] (dyslipidemia, obesity, diabetes, hypertension, smoking)</td>
</tr>
<tr>
<td>Younger age [7, 19–21, 41]</td>
</tr>
<tr>
<td>Absence of irradiation shields and protective techniques [7]</td>
</tr>
</tbody>
</table>

Protection of the heart during XRT

Mantle RT  
Involved Field RT  
Involved Node RT

Proportional Reduction in Mean Dose

Advantages of proton therapy

Gunderson and Tepper, Clinical Radiation Oncology. 2016.
Conformal RT approach and advantages of proton therapy

• A randomized pragmatic trial funded by PCORI
• **Aim:** To assess the effectiveness of proton vs. photon therapy in reducing major cardiovascular events (MCE)
• **Primary hypothesis:** For patients with locally advanced breast cancer, proton therapy will reduce the 10-year MCE rate after radiation from 6.3% to 3.8%
• **Sample size:** 1,716 patients
• **Accruing sites:** >30 proton centers and >50 participating radiation treatment centers across US
• **Large, simple trial approaches:** Passive and active follow-up techniques
Statins work to prevent myocardial injury through Anth-bC by regulating the production of nitric oxide (NO), regulating synthesis and restoring scavenging of superoxide free radicals (O$_2^-$). Question if statins can also mitigate the effect of radiation therapy.
Observational Study

- 628 women with breast cancer (BrC); Mean age 51.5 ± 10.8 years
- Followed for 2.55 ± 1.68 years
- Propensity matching 2:1
- 67 patients received statins and 134 controls received no statins
- Statin use was associated with lower risk for heart failure (HF)

Chart illustrates survival in statin users (red) and non-statin users (blue). Figures above abscissa relate to number surviving without heart failure at each 12 month interval.

PREVENT: NCI and NHLBI multi-center randomized, double-blind placebo controlled clinical trial testing the efficacy of generic atorvastatin among 250 women with stage I-III Breast Cancer scheduled to receive Anthracycline-based chemotherapy.
Potential suggestion for management of individuals previously receiving XRT

Unanswered questions related to cardio-protective strategies during XRT

• Do recently implemented cardioprotection strategies forestall the development of long-term cardiac sequelae?
• Are there adverse consequences from XRT exposure to other “non-heart” cardiovascular structures (e.g., the aorta)?
• Are there adverse, general systemic effects from the receipt of XRT that promote CVD (e.g., systemic inflammation)?
Potential myocardial ischemia after left breast XRT

<table>
<thead>
<tr>
<th>Years since breast cancer diagnosis</th>
<th>No. of deaths left versus right &amp; 95% CI</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of deaths left versus right &amp; 95% CI</td>
<td></td>
</tr>
<tr>
<td>Heart disease death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>2164/1972</td>
<td>700/633</td>
</tr>
<tr>
<td>5 - 9</td>
<td>1632/1479</td>
<td>521/442</td>
</tr>
<tr>
<td>10 - 14</td>
<td>806/758</td>
<td>281/197</td>
</tr>
<tr>
<td>15+</td>
<td>568/524</td>
<td>254/162</td>
</tr>
<tr>
<td>All other known causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>14775/13522</td>
<td>691/6516</td>
</tr>
<tr>
<td>5 - 9</td>
<td>8009/7863</td>
<td>3178/2990</td>
</tr>
<tr>
<td>10 - 14</td>
<td>3472/3343</td>
<td>1165/1095</td>
</tr>
<tr>
<td>15+</td>
<td>2106/2040</td>
<td>611/580</td>
</tr>
</tbody>
</table>

Fig. 5. Left-sided vs. right-sided breast cancer. Mortality ratios by radiotherapy status, cause, and years since diagnosis in 300,000 women with breast cancer and registered in the Surveillance Epidemiology and End Results (SEER) cancer registries, 1973 to 2001 (From Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective study of about 300,000 women in US SEER cancer registries. Lancet Oncol 2005;6:557-566; with permission.)

Cardiovascular disease associated with radiation treatment

- Lipid peroxidation
- Inactivation of other enzymes and proteins by incorporating tyrosine (nitrotyrosine)
- Activation of signaling pathways involving matrix metallo-proteinases that stimulate fibrosis and inflammation within the extracellular matrix
- Release of proapoptotic factors that mediate caspase dependent and independent cell death pathways and DNA fragmentation
- Overactivation of cell energy consuming cycles that deplete intracellular ATP pools

Myocardial injury
Contractile dysfunction
Heart failure

Antihypertensive
Antianginal
Antithrombotic
Improved reperfusion
Statins in breast cancer

- Desai, et al., Women’s Health Initiative
  - Study population of 154,587 women aged 50-79 years
  - 7,430 cases of BrC
  - Rate of BrC was 0.42% in statin users and 0.42% in non-statin users

- Ahern, et al., Danish Breast Cohort (n=66,000+)
  - Denmark on women with Stage I-III BrC
  - 18,769 participants receiving statins for primary or secondary prevention CAD
  - Simvastatin, a highly lipophilic statin, was associated with a reduced risk of BrC recurrence among participants, whereas no association between hydrophilic statin use and BrC recurrence was observed

Nitrotyrosine and statins

Figure 3: (A) Cardiac nytrotyrosine expression and (B) systolic LV function in 3 groups treated with placebo, Doxorubicin, and a combination of Fluvastatin and Doxorubicin. *Columns, mean; bars, SE. Dox, doxorubicin (Riad. Cancer Res. 2009.)
**Table: Comparison of Echocardiographic Parameters: Baseline vs. Follow-Up Values in Pilot Study**

<table>
<thead>
<tr>
<th>LVEF (%)</th>
<th>Statin Group (n=20)</th>
<th>Control Group (n=20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>61 ± 8</td>
<td>63 ± 7</td>
<td></td>
</tr>
<tr>
<td><strong>After 6 months</strong></td>
<td>63 ± 9</td>
<td>55 ± 10</td>
<td></td>
</tr>
<tr>
<td><strong>Mean change</strong></td>
<td>+1 ± 4</td>
<td>-8 ± 8</td>
<td>&lt;0.001</td>
</tr>
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</table>

In a recent study of 40 patients scheduled to receive Anth-bC, those randomized to receive atorvastatin (40 mg per day before and during Anth-bC) had no decrease in LVEF at 6 months, but those randomized to receive Anth-bC without statins had an 8% reduction in LVEF.

In a multivariable model adjusted for age, gender, comorbidities, and the anthracycline dose, those who received statin had an LVEF decline of -0.5% compared to the non-statin group at -7.8%.

![Baseline to 6-month change in LVEF](image)
CVD and cancer survivor mortality