Cardiotoxic Effects of Chemotherapy on Pediatric and Adult Survivors of Cancer

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CARDIOTOXIC EFFECTS OF CHEMOTHERAPY ON PEDIATRIC AND ADULT SURVIVORS OF CANCER; WHAT’S NEW IN DIAGNOSIS AND TREATMENT

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Dr S Virani
Disclosure

- I have no conflict of interest
- No commercial interests
- Nothing to disclose

Best reference:
- Review article

Franco V.I. Cardiovascular effects in childhood cancer survivors treated with anthracyclines. Cardiol Res Pract 2011;Feb 10;2011: 134679
“Oncologists” Definition of cardiotoxicity

<table>
<thead>
<tr>
<th>LV systolic dysfunction</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCAE v 3.0</td>
<td>Asymptomatic EF &gt;49% SF &gt;23%</td>
<td>Asymptomatic EF &lt;50% &gt;39% SF &lt;24%&gt;14%</td>
<td>Symptomatic EF&lt;39% &gt;19% SF&lt;15%</td>
<td>Refractory CHF EF&lt;20%</td>
</tr>
<tr>
<td>CTCAE v 4.0</td>
<td>Not graded</td>
<td>Asymptomatic EF &lt;50% &gt;39% Or 10-19% decline from baseline</td>
<td>Symptomatic EF&lt;39% &gt;19% Or 20% decline from baseline</td>
<td>Refractory CHF EF&lt;20%</td>
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<tr>
<td>Does not use SF</td>
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In our study of pts with Ewing sarcoma % decline with normal EF during therapy did not predict for late toxicity (Pediatr Blood Cancer 2013;60:842-8)
Chemotherapy induced Cardiotoxicity

Pfeffer B. Br J Cardiol 2009;16:85-9
Sheppard RJ. Front Pharmacol 2013;4 (19):1-10

Anthracyclines
Doxorubicin; Daunorubicin, Epirubicin, Idarubicin, Mitoxantrone

Monclonal antibodies
Trastuzumab, Bevacuzimab,

Tyrosine kinase inhibitors
Sunitinib;

Fluoropyrimidines
5 FU; Capecitabine
Equivalence ratios of anthracyclines

- BCCA data based on equi-myelotoxicity
- DAUNOrubicin x 0.5-0.83  DOXOrubicin x 1
- epirubicin x 0.5-0.67  IDArubicin x 2-5
- mitoxantrone x 2.2-4

However for equimyelotoxic doses epirubicin and daunomycin appear less cardiotoxic

Ref. Smith LA. BMC Cancer 2010;June 29;10:337
Lieke E. Abstr Equivalence ratio for daunomycin to doxorubicin in relation to late heart failure
European Symposium Late complications Edinburgh Sept 2014
Risk factors for anthracycline cardiotoxicity

- Delayed onset: Risk increases over time
- Dose of anthracyclines (adults) >400mg/m²
- Young age
  children no “safe” dose
- Females
- Mediastinal radiation
- Cyclophosphamide
- Obesity
- Diabetes
- Hypertension
- Large Bolus administration
- Genetic factors

Adult data

Source: Br J Cardiol © 2009 Sherbourne Gibbs, Ltd.
Chemotherapy (anthracyclines)

- Myocardial Disease – Increasing doses result in progressive loss of myocardial cells.
- Effects are much more severe in children whose hearts are still growing.

Cardiovascular Effects in Childhood Cancer Survivors Treated with Anthracyclines


Cumulative incidence (%) of Congestive heart failure over time since diagnosis (years) for different doses of anthracyclines: >250mg/m², <250mg/m², none.
Genetic factors

Individuals exposed to high-dose (>250 mg/m²) anthracyclines, the rs2232228 AA genotype, in the hyaluronan synthase 3 (HAS3) gene conferred an 8.9-fold increased cardiomyopathy risk compared to the GG genotype. *Wang X J Clin Oncol 2014;32:647-53*

SLC28A3 (protective) and UGT1A6 (increased risk) predict for anthracycline cardiotoxicity. *Visscher H Pediatr Blood Cancer 2013;60:375-81*

**Anthracycline risk groups:**

- Combining clinical and genetic factors in a multimarker regression model identifies three risk groups for anthracycline induced cardiotoxicity.
Cardiotoxicity highest in first year & continues to increase over time in high risk groups

36% of high risk group patients develop serious cardiotoxicity in the 1st year; of these 24% developed heart failure

\( P_{\text{trend}} = 6.7 \times 10^{-25} \)
Predictors for Anthracycline toxicity

TROPONIN +VE PATIENTS ONE MONTH POST ANTHRACYCLINE PREDICTS FOR TOXICITY

Source: Br J Cardiol © 2009 Sherbourne Gibbs, Ltd.
Protective Effect of ACE Inhibitors In Troponin +ve Pts

Key: ACEI = angiotensin-converting enzyme inhibitor; HDC = high-dose chemotherapy

Source: Br J Cardiol © 2009 Sherbourne Gibbs, Ltd.
Protective factors for anthracycline cardiotoxicity

- ACE Inhibitors
- Dexrazoxane
  (mucositis myelosuppression)
- Angiotensin antagonists

Ref Kalam K
Eur J Cancer 2013;49:2900-9

- Exercise and “Healthy Heart Program”

  Transitioning children to adult care

- Follow up The VGH&UBC Cardio-Oncology Clinic
  Vancouver
- Tel 604-875-5264 Fax 604-875-5906
Screening for anthracycline cardiotoxicity

**Surveillance:**
- Echocardiogram (FS<28%;EF<50%),
- ECG(QTc >480ms)
- Troponins (troponin I)

*(Curigliano G. Ann Oncol 2012; Suppl 7 vii155-vii66)*

**Early Treatment**
- ACE inhibitors, Beta blockers delays progression of cardiac failure *(Colombo A. Curr Treat Options Cardiovasc Med 2014;16:313)*

**Cost-effectiveness of COG Guidelines**
- Less frequent screening more cost effective maintain 80% of benefits *(Wong FL Ann Intern Med 2014;160;672-83)*