Prevention of Anthracycline-induced Cardiotoxicity

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Cancer and the Heart

- Nearly 12 million cancer survivors in U.S. in 2012
- 67% of people diagnosed with cancer today will be alive in 5 years
- 75% of children diagnosed with cancer today will be alive in 10 years

- Cancer treatments (chemotherapy or radiation) can lead to short and long-term cardiovascular complications
Causes of Death in Cancer Survivors

- National Health and Nutrition Examination Surveys (NHANES) presented at AACR in March 2012
- 1807 cancer survivors; median follow-up time: 7 years
Onco-Cardiology

A cardiovascular sub-specialty focused on identifying, preventing, and treating cardiovascular complications of cancer therapy

www.cancerandtheheart.org
## Chemotherapy-induced Cardiotoxicity

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Incidence, %</th>
<th>Frequency of Use</th>
<th>Chemotherapy Agents</th>
<th>Incidence, %</th>
<th>Frequency of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td></td>
<td></td>
<td>Monoclonal antibody–based tyrosine kinase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin)</td>
<td>3-26</td>
<td>+++</td>
<td>Bevacizumab (Avastin)</td>
<td>1.7-3</td>
<td>++</td>
</tr>
<tr>
<td>Epirubicin (Ellence)</td>
<td>0.9-3.3</td>
<td>++</td>
<td>Trastuzumab (Herceptin)</td>
<td>2-28</td>
<td>+++</td>
</tr>
<tr>
<td>Idarubicin (Idamycin PFS)</td>
<td>5-18</td>
<td>+</td>
<td>Proteasome inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide (Cytoxan)</td>
<td>7-28</td>
<td>+++</td>
<td>Bortezomib (Velcade)</td>
<td>2-5</td>
<td>++</td>
</tr>
<tr>
<td>Ifosfamide (Ifex)</td>
<td>17</td>
<td>+++</td>
<td>Dasatinib (Sprycel)</td>
<td>2-4</td>
<td>++</td>
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<tr>
<td>Antimetabolites</td>
<td></td>
<td></td>
<td>Imatinib mesylate (Gleevec)</td>
<td>0.5-1.7</td>
<td>+</td>
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<tr>
<td>Clofarabine (Clolar)</td>
<td>27</td>
<td>+</td>
<td>Lapatinib (Tykerb)</td>
<td>1.5-2.2</td>
<td>+</td>
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<tr>
<td>Antimicrotubule agents</td>
<td></td>
<td></td>
<td>Sunitinib (Sutent)</td>
<td>2.7-11</td>
<td>+++</td>
</tr>
<tr>
<td>Docetaxel (Taxotere)</td>
<td>2.3-8</td>
<td>++</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Yeh ET, Bickford CL. *J Am Coll Cardiol.* 2009;53:2231-2247
Congestive heart failure vs. cumulative dose of doxorubicin

Von Hoff, Ann Int Med 91:710-17, 1979
Early Detection of Cardiotoxicity

Doxorubicin was given IV every 3 to 4 weeks. Biopsy specimens were taken approximately 3 weeks following last therapy.

Anthracycline-induced cardiotoxicity starts from the first dose
Doxorubicin poisons Topoisomerase 2 (Top2) causes DNA double strand breaks (DSBs) leads to apoptosis
Old Paradigm: Two Distinct Pathways

Doxorubicin

- Reactive oxygen species → Cardiotoxicity
- Topoisomerase II → Kills Cancer Cells
Anthracycline cardiotoxicity: “ROS and iron hypothesis”

[Diagram showing the mechanism of ROS and iron in cardiac toxicity]
## Limitations of the ROS/Fe Hypothesis

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>ROS generation</th>
<th>Fe chelation</th>
<th>Top2 inhibition</th>
<th>Preventing Cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-acetylcysteine</td>
<td>Block</td>
<td>No</td>
<td>No</td>
<td>No effect</td>
</tr>
<tr>
<td>ICRF-161</td>
<td>?</td>
<td>Yes</td>
<td>No</td>
<td>No effect</td>
</tr>
<tr>
<td>Dexrazoxane</td>
<td>Block</td>
<td>Yes</td>
<td>Yes</td>
<td>Prevent</td>
</tr>
</tbody>
</table>
Two different Top2: $\alpha$ and $\beta$

Doxorubicin poisons both Top2$\alpha$ and Top2$\beta$.

Proliferating cells express Top2$\alpha$.

However, the adult heart only expresses Top2$\beta$.

New Hypothesis

Doxorubicin-induced cardiotoxicity is mediated by Top2$\beta$. 
Construction of conditional cardiomyocyte-specific top2β knockout mice
Deletion of Top2β from Adult Heart

Tamoxifen-MHC-cre Top2β<sup>flox/flox</sup> → Top2β<sup>Δ/Δ</sup>
Doxorubicin

Topoisomerase IIβ

DNA double strand break

Cell Death
Is there still a role for the ROS hypothesis?
Doxorubicin-induced ROS production is Top2β-dependent
Top2β is required for doxorubicin-induced ROS production

Doxorubicin

\[ \downarrow \]

Topoisomerase IIβ

\[ \downarrow \]

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Reactive Oxygen Species
Doxorubicin & Topoisomerase IIβ

Reduction in thioredoxin, peridoredoxin, superoxide dismutase

Increase in ROS
Doxorubicin & Topoisomerase IIβ

PGC1α & PGC1β
Doxorubicin-induced mitochondrial change is Top2β-dependent
Topoisomerase 2b + doxorubicin

Changes in transcriptome

Mitochondrial dysfunction & Reactive oxygen species

DNA double strand breaks

Cardiotoxicity
Chronic doxorubicin-cardiotoxicity model

To delete Top2β in cardiomyocytes
Top2β deletion prevents doxorubicin-cardiotoxicity
Identification of the molecular basis of doxorubicin-induced cardiotoxicity

Sui Zhang\textsuperscript{1}, Xiaobing Liu\textsuperscript{2,3}, Tasneem Bawa-Khalfe\textsuperscript{1}, Long-Sheng Lu\textsuperscript{2}, Yi Lisa Lyu\textsuperscript{4}, Leroy F Liu\textsuperscript{4} & Edward TH Yeh\textsuperscript{1,2}

Doxorubicin is believed to cause dose-dependent cardiotoxicity through redox cycling and the generation of reactive oxygen species (ROS). Here we show that cardiomyocyte-specific deletion of Top2b (encoding topoisomerase-II\textbeta) protects cardiomyocytes from doxorubicin-induced DNA double-strand breaks and transcriptome changes that are responsible for defective mitochondrial biogenesis and ROS formation. Furthermore, cardiomyocyte-specific deletion of Top2b protects mice from the development of doxorubicin-induced progressive heart failure, suggesting that doxorubicin-induced cardiotoxicity is mediated by topoisomerase-II\textbeta in cardiomyocytes.

18:1639-1642, 2012
Mechanism-based cardioprotection

Use $\text{Top2}^\alpha$-specific drugs to treat cancer

Use $\text{Top2}^\beta$ to predict doxorubicin sensitivity

Inhibit $\text{Top2}^\beta$ to achieve primary prevention
**Doxorubicin-Sensitive**

doxorubicin exposure <250 mg/m² and reduced EF (<50%)

**Doxorubicin-Resistant**

doxorubicin exposure > 450 mg/m² and preserved EF (>50%)
Top2β level in blood and doxorubicin sensitivity
Cardio-protection by dexrazoxane

Chelates iron (not important)

Inhibition and degradation of Top2β

Effective in preventing doxorubicin-induced cardiotoxicity
Know thyself,
Know thy enemy,
Fight a hundred battles, and win them all.

Sun Tze