Anthracycline Cardiotoxicity

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Bernard Fishman Professor of Clinical Medicine
at the Abramson Cancer Center of the University
of Pennsylvania
Anthracyclines: Cornerstone of Rx of Childhood and Adult Cancer

<table>
<thead>
<tr>
<th>Carcinoma</th>
<th>Leukemia</th>
<th>Lymphoma</th>
<th>Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast, small cell lung,</td>
<td>Acute lymphoblastic</td>
<td>Hodgkin</td>
<td>Soft tissue</td>
</tr>
<tr>
<td>urinary track, GI, GYN,</td>
<td>Acute myeloblastic</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Ewing</td>
</tr>
<tr>
<td>thyroid</td>
<td></td>
<td>Cutaneous T-cell lymphoma</td>
<td>Osteo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neuroblastoma</td>
</tr>
</tbody>
</table>

Adapted from Henriksen Heart 2018;104:971
“Cardio-Friendly” or Cardiotoxic?
“Cardio-Friendly” or Cardiotoxic?
Anthracline Cardiotoxicity: Incidence

Swain / MD Anderson
Von Hoff

Percent congestive heart failure

Cumulative doxorubicin dosage

450mg

Von Hoff. Ann Int Med 1979
Swain. Cancer 2003
Fig. 1

Anthracline Cardiotoxicity: Incidence

Realistic Approximations

Overt CHF

(Cumulative dose mg/m²)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 240</td>
<td>2-3%</td>
</tr>
<tr>
<td>Up to 450</td>
<td>5%</td>
</tr>
</tbody>
</table>

Von Hoff, Ann Int Med 1979
Swain. Cancer 2003
Anthracline Cardiotoxicity: Incidence

Risk:
- Dose dependent
- Increases over time
- Marked individual variation
- Not zero even at ≤100mg/m²

Von Hoff. Ann Int Med 1979
Swain. Cancer 2003
Asymptomatic Cardiotoxicity is More Prevalent

## Anthracyclines: Cornerstone of Rx of Childhood and Adult Cancer

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<td>Hodgkin</td>
<td>Soft tissue</td>
</tr>
<tr>
<td>lung, urinary</td>
<td>Acute myeloblastic</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Ewing</td>
</tr>
<tr>
<td>track, GI, GYN,</td>
<td></td>
<td>lymphoma</td>
<td>Osteo</td>
</tr>
<tr>
<td>thyroid</td>
<td></td>
<td>Cutaneous T-cell lymphoma</td>
<td>Neuroblastoma</td>
</tr>
</tbody>
</table>

### Adjuvant Therapy

- **“AC”** 240 mg/m²
- Liposomal doxorubicin: 30 mg/m²/cycle

*Adapted from Henriksen Heart 2018;104:971*
Anthracyclines: Cornerstone of Rx of Childhood and Adult Cancer

<table>
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<tbody>
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</tr>
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<td></td>
<td>Acute myeloblastic</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Ewing</td>
</tr>
</tbody>
</table>

“7+3” Induction
Daunorubicin: 135 mg/m²
Idarubicin 36 mg/m²
Mitoxantrone 21 mg/m²
Vyxeos™: 44 mg/m² x 3
(Consolidation Vyxeos 29 mg/m² x 2)
Anthracyclines: Cornerstone of Rx of Childhood and Adult Cancer

<table>
<thead>
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<th>Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast, small cell lung, urinary tract</td>
<td>Acute lymphoblastic</td>
<td>Hodgkin</td>
<td>Soft tissue</td>
</tr>
<tr>
<td>(kidney, ovary)</td>
<td>Acute myeloblastic</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Ewing</td>
</tr>
<tr>
<td>(testes)</td>
<td></td>
<td></td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>(bladder, stomach)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CHOP**: doxorubicin 50 mg/m²/cycle

**ABVD**: doxorubicin 50 mg/m²/cycle (25 mg/m² x 2)

Stanford V-same as ABVD dosing

Adapted from Henriksen Heart 2018;104:971
## Anthracyclines: Cornerstone of Rx of Childhood and Adult Cancer

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<td>Acute lymphoblastic Acute myeloblastic</td>
<td>Hodgkin Non-Hodgkin’s lymphoma Cutaneous T-cell lymphoma</td>
<td>Soft tissue Ewing Osteo Neuroblastoma</td>
</tr>
</tbody>
</table>

Doxorubicin 75 mg/m$^2$ per cycle

Adapted from Henriksen Heart 2018;104:971
# Anthracycline Equivalence Doses

<table>
<thead>
<tr>
<th>Group or Study</th>
<th>Doxorubicin*</th>
<th>Daunorubicin</th>
<th>Idarubicin</th>
<th>Epirubicin</th>
<th>Mitoxantrone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children’s Oncology Group^10^-12</td>
<td>1</td>
<td>1†</td>
<td>5</td>
<td>0.67</td>
<td>4</td>
</tr>
<tr>
<td>Bristol Royal Hospital for Sick Children^13</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>AML Collaborative Group^14</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Kyushu University, Fukuoka, Japan^15</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Taiwan Pediatric Oncology Group^16</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Childhood Cancer Survivor Study^2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch Childhood Oncology Group LATER^3</td>
<td>1</td>
<td>1</td>
<td></td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Sookmyung Women’s University, Seoul, Korea^17‡</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
<td>0.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myelocytic leukemia; LATER, Longterm Effects of Childhood Cancer (Lange Termijn Effecten Kinderkanker).

*Reference value (except AML Collaborative Group, which used daunorubicin ratio of 1 as the reference value).
†Ratio of 1 reported in the current Children’s Oncology Group guidelines, version 4, October 2013; previous versions used a ratio of 0.83.
‡All ratios listed are based on hematologic toxicity equivalence rather than cardiotoxicity with the exception of Sookmyung Women’s University, which uses ratios that are based on the ratio proposed by Keefe.\(^18\)

Feijen EAM. J Clin Oncol 2015;33:3774
# Anthracycline Equivalence Doses

## Table 1. Anthracycline Toxicity Equivalence Ratios Used in Various Cooperative Groups and Cohort Studies for Assessment of Cardiotoxicity

<table>
<thead>
<tr>
<th>Group or Study</th>
<th>Doxorubicin*</th>
<th>Daunorubicin</th>
<th>Idarubicin</th>
<th>Epirubicin</th>
<th>Mitoxantrone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children’s Oncology Group&lt;sup&gt;10-12&lt;/sup&gt;</td>
<td>1</td>
<td>1&lt;sup&gt;†&lt;/sup&gt;</td>
<td>5</td>
<td>0.67</td>
<td>4</td>
</tr>
<tr>
<td>Bristol R (2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML Cooperative Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyushu University</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan Pediatric Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood Cancer Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch Childhood Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sookmyung University</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Abbreviations            | *Refer to Reference 10.  
†Ratio of 1 for Doxorubicin/Idarubicin.  
‡All ratios are for the unit mg/m² per cycle.  
§Ratios in this table are calculated using ratios that are based on the ratio proposed by Keefe. | |

**Doxorubicin/Daunorubicin 1 mg**

**Idarubicin**

**Epirubicin**

**Mitoxantrone**

Feijen EAM. *J Clin Oncol* 2015;33:3774
Anthracyclines: Anti-cancer Mechanism of Action

Interference with DNA Replication & Transcription

Malignant Cell Death
Anthracyclines: Anti-cancer Mechanism of Action

Interference with DNA Replication & Transcription

Intercalation & Enzyme inhibition: (Topoisomerase 2α)

Free radical generation
Anthracycline Cardiotoxicity: Possible Mechanisms
Doxorubicin

Mito/SR Calcium/Iron Overload

ROS

Lipid peroxidation
DNA damage
Cellular dysfunction
Apoptosis

Cell Death Ventricular Remodeling CARDIOMYOPATHY

Energy depletion

Inhibits DNA uncoiling
Double stand breaks
Historical Spectrum: Anthracycline Cardiotoxicity

• During or post first infusion: ACUTE
• Weeks-12 months: SUBACUTE
• Beyond 12 months: LATE
Historical Spectrum
Anthracycline Cardiotoxicity

- During or immediate after infusion: ACUTE
- Weeks-12 months: SUBACUTE
- Beyond 12 months: LATE
Anthracycline Cardiotoxicity: A Continuous Process

- Start of Anthracycline Chemotherapy
- Hours/Days/Weeks
- Months
- Years
- Myocardial Cell injury
- Asymptomatic Cardiotoxicity
- Overt Cardiotoxicity

Adapted from Cardinale et al. Curr Cardiol Rep 2016:18:51
Myocardial Cell injury

Myocardial Deformation

Asymptomatic Cardiotoxicity

Overt Cardiotoxicity

Hours/Days/Weeks

Months

Years

Start of Anthracycline Chemotherapy

MARKER

Increase in Troponin

Decrease in GLS

Decrease in LVEF

HF Symptoms

Adapted from Cardinale et al. Curr Cardiol Rep 2016:18:51
“High” Risk

- Age
- Sex
- Pre-existing CV disease & risk factors
- Cumulative anthracycline dose
- Mediastinal radiation
- Additional cardiotoxic treatment
- Genetic (UGT1A6, ABCC1, ABCC1, HNMT; SLC28A3, HFE, CBR3, RARG, CELF4, HAS3, C28Y HFE)
Risk Prediction Scores

**Table 3. CHF Risk Scores and Corresponding Model Discrimination and Predictive Power**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Simple Model†</th>
<th>Standard Model</th>
<th>Heart Disease Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Age at diagnosis, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5-9</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>10-14</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>≥ 15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Anthracycline, mg/m²</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>100-249</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥ 250</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Chest or heart RT, Gy</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5-14</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>15-34</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥ 35</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

**Cohort**

<table>
<thead>
<tr>
<th>CCSS (n = 2859)</th>
<th>AUC</th>
<th>C-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>0.71</td>
<td>0.74</td>
</tr>
<tr>
<td>C-statistic</td>
<td>0.72</td>
<td>0.76</td>
</tr>
<tr>
<td>EKZ/AMC (n = 26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>0.74</td>
<td>0.81</td>
</tr>
<tr>
<td>C-statistic</td>
<td>0.75</td>
<td>0.80</td>
</tr>
<tr>
<td>NWTS (n = 49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>0.76</td>
<td>0.72</td>
</tr>
<tr>
<td>C-statistic</td>
<td>0.79</td>
<td>0.82</td>
</tr>
<tr>
<td>SJLIFE (n = 19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>0.63</td>
<td>0.68</td>
</tr>
<tr>
<td>C-statistic</td>
<td>0.63</td>
<td>0.68</td>
</tr>
</tbody>
</table>

**Abbreviations:** AUC, area under the curve; C, concordance; CCSS, Canadian Cardiovascular Study; CHF, congestive heart failure.

**Delivery recommendations**

<table>
<thead>
<tr>
<th>1. Risk assessment</th>
<th>Patient-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication-related risk</td>
<td>Cardiomyopathy or heart failure</td>
</tr>
<tr>
<td>High (risk score 4): Anthracyclines, Cyclophosphamide, Ifosfamide, Chlorambucil, Herceptin</td>
<td>CAD or equivalent (incl. PAD)</td>
</tr>
<tr>
<td>Intermediate (risk score 2): Docetaxel, Pertuzumab, Sunifer, Sorafenib</td>
<td>HTN</td>
</tr>
<tr>
<td>Low (risk score 1): Bevacizumab, Cetuximab, Imatinib, Lapatinib</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Rare (risk score 0): For example: Etoposide, Rituximab, Thalidomide</td>
<td>Prior or concurrent chemotherapy</td>
</tr>
</tbody>
</table>

**Overall risk by Cardiotoxicity Risk Score (CRS)**

(risk categories by drug-related risk score plus number of patient-related risk factors: CRS = 0: very low, 1-2: low, 3-4: intermediate, 5-6: high, 7-8: very high)

**Monitoring recommendations**

| Very high cardiotoxicity risk: TTE with stress before every (other) cycle and 3-6 months and 1 year after chemotherapy. Atrial ECG, cTn with TTE during chemotherapy. | Atrial ECG, cTn at the end of chemotherapy |
| High cardiotoxicity risk: TTE with stress every 3 cycles, and 3-6 months and 1 year after chemotherapy. Atrial ECG, cTn with TTE during chemotherapy. | Very low cardiotoxicity risk: None |
| Intermediate cardiotoxicity risk: TTE with stress mid-term and 3-6 months after chemotherapy. Atrial ECG, cTn at the end of chemotherapy. | Very low cardiotoxicity risk: None |

**Management recommendations**

| Very high cardiotoxicity risk: Initiate ACE-I/ARB if renal function is stable as close to dose as tolerated. | Non-cardiac risk factors, e.g., hypertension, diabetes, renal function, etc. |
| High cardiotoxicity risk: Initiate ACE-I/ARB, and/or optimize renal function. | Non-cardiac risk factors, e.g., hypertension, diabetes, renal function, etc. |
| Intermediate cardiotoxicity risk: Discuss risk and benefit of medications. | Non-cardiac risk factors, e.g., hypertension, diabetes, renal function, etc. |
| Low cardiotoxicity risk: None, monitoring only. | Non-cardiac risk factors, e.g., hypertension, diabetes, renal function, etc. |
| Very low cardiotoxicity risk: None, monitoring only. | Non-cardiac risk factors, e.g., hypertension, diabetes, renal function, etc. |
“Future” Risk Prediction Scores

“Clinico-genetic”

Strain Alone

Visscher H. J Clin Oncol 2012;30:1422

Myocardial Cell injury

Asymptomatic Cardiotoxicity

Overt Cardiotoxicity

Start of Anthracycline Chemotherapy

Hours/Days/Weeks

Months

Years

Myocardial Deformation

Decrease in GLS

Decrease in LVEF

HF Symptoms

STAGE A

STAGE B

STAGE C/D

Increase in Troponin

Decrease in LVEF

Adapted from Cardinale et al. Curr Cardiol Rep 2016:18:51
How Can We Prevent Progression From Stage A to Stage B?
Myocardial Cell injury

Asymptomatic Cardiotoxicity

Overt Cardiotoxicity

Increase in Troponin

Decrease in GLS

Decrease in LVEF

HF Symptoms

Alternative regimen
Lower dosing
Infusion dynamics
Different formulation
Dexrazoxane
CV RF management

STAGE A
PRIMARY PREVENTION

STAGE B

STAGE C/D

Adapted from Cardinale et al. Curr Cardiol Rep 2016:18:51
How Can We Prevent Short-term Progression From Stage B to Stage C/D Short Term?
Myocardial Cell injury
Myocardial Deformation
Asymptomatic Cardiotoxicity
Overt Cardiotoxicity

Hours/Days/Weeks
Months
Years

START A

Myocardial Deformation
Decrease in GLS
Decrease in LVEF
HF Symptoms

STAGE B

Myocardial Cell injury
Increase in Troponin

STAGE A

SECONDARY PREVENTION: Surveillance & Treatment
- Biomarkers & Imaging
- Early intervention

Adapted from Cardinale et al. Curr Cardiol Rep 2016:18:51
• Some combination of ↑troponin and ↓GLS predicts late change in LVEF\textsuperscript{1,2,3}
• Early treatment may lead to LVEF recovery in up to 82% of patients\textsuperscript{4}
• Late MACEs are inversely proportional to LVEF recovery\textsuperscript{4}

2. Ky J Amer Col Cardiol 2014
3. Sawaya Amer J Cardiol 2011
4. Cardinale J Amer Col Cardiol 2010
• Probably no difference between pharmacologic primary prevention in all versus triggered secondary prevention\(^1\)
• Lots of unanswered questions

1. Cardinale Europ J Oncol 2018
There is Nothing New Under the Sun

There was no significant difference in EF% between the Carvedilol group and the Control group (P = 0.3). However, there was a significant difference between the Carvedilol group and the Control group (P = 0.001).

Kalay N, JACC 2006;48:2258
How Can We Prevent Long-term Progression From Stage A to Stage C/D?
**STAGE A**
- Start of Anthracycline Chemotherapy
- Myocardial Cell injury
  - Increase in Troponin

**STAGE B**
- Myocardial Deformation
  - Decrease in GLS

**STAGE C/D**
- Asymptomatic Cardiotoxicity
  - Decrease in LVEF
- Overt Cardiotoxicity
  - HF Symptoms

**LATE PREVENTION/MONITORING GUIDELINES?**

Adapted from Cardinale et al. *Curr Cardiol Rep* 2016:18:51
Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group
<table>
<thead>
<tr>
<th>General recommendations</th>
<th>Survivors treated with anthracyclines or chest radiation or both and their healthcare providers should be aware of the risk of cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who needs cardiomyopathy surveillance?</td>
<td></td>
</tr>
<tr>
<td><strong>Patients treated with anthracyclines</strong></td>
<td>Cardiomyopathy surveillance is recommended for survivors treated with high dose (≥250 mg/m²) anthracyclines</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathy surveillance is reasonable for survivors treated with moderate dose (100 to &lt;250 mg/m²) anthracyclines</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathy surveillance may be reasonable for survivors treated with low dose (&lt;100 mg/m²) anthracyclines</td>
</tr>
<tr>
<td><strong>Patients treated with chest radiation</strong></td>
<td>Cardiomyopathy surveillance is recommended for survivors treated with high dose (≥35 Gy) chest radiation</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathy surveillance may be reasonable for survivors treated with moderate dose (15 to &lt;35 Gy) chest radiation</td>
</tr>
<tr>
<td></td>
<td>No recommendation can be formulated for cardiomyopathy surveillance for survivors treated with low dose (&lt;15 Gy) chest radiation with conventional fractionation</td>
</tr>
<tr>
<td><strong>Patients treated with anthracyclines + chest radiation</strong></td>
<td>Cardiomyopathy surveillance is recommended for survivors treated with moderate to high dose anthracyclines (≥100 mg/m²) and moderate to high dose chest radiation (≥15 Gy)</td>
</tr>
<tr>
<td>Question</td>
<td>Recommendation</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>What surveillance modality should be used?</strong></td>
<td>Echocardiography is recommended as the primary cardiomyopathy surveillance modality for assessment of left ventricular systolic function in survivors treated with anthracyclines or chest radiation</td>
</tr>
<tr>
<td>Radionuclide angiography or cardiac MRI may be reasonable for cardiomyopathy surveillance in at-risk survivors for whom echocardiography is not technically feasible or optimal. Assessment of cardiac blood biomarkers (e.g., natriuretic peptides) in conjunction with imaging studies may be reasonable in instances where symptomatic cardiomyopathy is strongly suspected or in individuals who have borderline cardiac function during primary surveillance.</td>
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<tr>
<td>Assessment of cardiac blood biomarkers is not recommended as the only strategy for cardiomyopathy surveillance in at-risk survivors.</td>
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</tr>
<tr>
<td><strong>At what frequency should surveillance be performed for high risk survivors?</strong></td>
<td>Cardiomyopathy surveillance is recommended for high risk survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis and continued every 5 years thereafter.</td>
</tr>
<tr>
<td>More frequent cardiomyopathy surveillance is reasonable for high risk survivors.</td>
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<tr>
<td>Lifelong cardiomyopathy surveillance may be reasonable for high risk survivors.</td>
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</tr>
<tr>
<td><strong>At what frequency should surveillance be performed for moderate or low risk survivors?</strong></td>
<td>Cardiomyopathy surveillance is reasonable for moderate and low risk survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis and continue every 5 years thereafter.</td>
</tr>
<tr>
<td>More frequent cardiomyopathy surveillance may be reasonable for moderate and low risk survivors.</td>
<td></td>
</tr>
<tr>
<td>Lifelong cardiomyopathy surveillance may be reasonable for moderate and low risk survivors.</td>
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</tbody>
</table>
INITIAL CLINICAL ASSESSMENT FOR PATIENTS WHO HAVE RECEIVED PREVIOUS ANTHRACYCLINE THERAPY

- History and physical
  - Assess for signs and symptoms of heart failure\(^a\)\(^d\)
  - Assess patient's ability to perform routine and desired activities of daily living
  - Look for signs of volume overload
- Evaluate for presence of heart failure risk factors
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Family history of cardiomyopathy
  - Age >65 years
  - High cumulative anthracycline dose (ie, cumulative doxorubicin dose at or higher than 260 mg/m\(^2\) or equivalent)
  - Low-normal LVEF (50\%–54\%) at baseline
  - History of other cardiovascular comorbidities (ie, atrial fibrillation, known coronary artery disease [CAD], baseline evidence of structural heart disease)
  - Smoking
  - Obesity
  - Review medications, alcohol use, and other substance use
  - Review oncologic history
    - Review total cumulative dose of anthracycline
    - Other systemic therapy\(^b\) and/or chest radiation therapy

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\(^a\) Signs and symptoms of heart failure include: Shortness of breath or chest pain after physical activity or exercise, shortness of breath when sleeping, waking up at night or only at night, shortness of breath at rest, fatigue, cold sweats, and a rapid or irregular heartbeat.

\(^b\) Other systemic therapy includes chemotherapy, targeted therapy, or immunotherapy.

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Cardiovascular risk factor management\(^c\)
- Consider two-dimensional echocardiogram (ECHO) with Doppler flow study for survivors with one or more risk factors within 1 year after completion of anthracycline therapy\(^d\).

No evidence of structural heart disease, but symptomatic\(^a\)
- Workup for other causes of symptoms
  - Referral to other specialties (eg, pulmonology or cardiology)

No evidence of structural heart disease and asymptomatic
- See Stage A (SCARDIO-3)

Evidence of structural heart disease (asymptomatic or symptomatic\(^3\)):
  - Left ventricular (LV) dysfunction
  - LV hypertrophy
  - Valvular disease
  - LV dilatation and/or wall thinning

Determine stage of cardiomyopathy (heart failure)
(See SCARDIO-3)

ALL “Guidelines” recognize potential protective effects of prophylactic BB, ACE/ARB (small trials) but no robust data & no recommendations.
A 45 year old male was diagnosed with cervical Hodgkin’s lymphoma at age 18 years. He was treated with multi-agent chemotherapy that included 360 mg/m2 of doxorubicin. He has a background of poorly controlled hypertension. He now presents with pulmonary edema. Which of the following is not a likely cause of his presentation?
A. Pulmonary hypertension from prior lymphoma
B. Acute coronary ischemia
C. Uncontrolled hypertension
D. Anthracycline cardiomyopathy
Anthracyclines

Take Home Messages

• Anthracyclines are potent chemotherapeutic drugs that can also cause cardiotoxicity.
• Cardiotoxicity is a continuous process that begins with exposure that may evolve over time.
• Cardiotoxicity has been most frequently defined by a reduction in LVEF.
Take Home Messages

• Although there is a dose dependent relationship to cardiotoxicity, there is no safe anthracycline dose

• Asymptomatic cardiotoxicity is more common than symptomatic disease

• Early detection and intervention may impact progression, partial recovery and outcome

• Aggressive survivor risk factor management is the only true evidence-based intervention