Cardio-Oncology: Cardiac care specific to cancer patients and survivors

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Learning Objectives:
• Discuss cardiotoxicity associated with breast cancer therapies: anthracyclines and trastuzumab
• Discuss cardiovascular risk in patients with prostate cancer on androgen deprivation therapy
• Introduce the Children’s Oncology Group guidelines as a useful clinical tool when caring for survivors of childhood cancer
• Introduce the American Society of Clinical Oncology cardiotoxicity clinical guideline

Management of cardiac conditions in patients undergoing cancer treatment and in cancer survivors

CARDIO-ONCOLOGY
Figure 1. Percent distribution of the 10 leading causes of death, by sex: United States, 2014

1. Cancer ranked 1st (22.5% of deaths) for males and 2nd (21.6% of deaths) for females.
2. Heart disease ranked 2nd for males (17.7%) and 4th for females (13.0% of deaths).
3. Chronic lower respiratory diseases ranked 4th for males (4.3%) and 5th for females (2.7% of deaths).
4. Stroke ranked 5th for males (5.2%) and 6th for females (3.9% of deaths).
5. Alzheimer's disease ranked 6th for males, accounting for 3.6% of deaths.
6. Diabetes mellitus ranked 7th for males, accounting for 5.0% of deaths.
7. Chronic liver disease and cirrhosis ranked 8th for males (6.0%) and 7th for females (7.4% of deaths).
8. Septicemia ranked 9th for males (1.8% of deaths) and 10th (1.6% of deaths) for females.
9. Kidney disease ranked 9th for males (2.5% of deaths), but it was not ranked among the 10 leading causes for females.
10. Suicide ranked seventh for males (2.0% of deaths) but eighth for females (2.2% of deaths).

In 2014, the leading cause of death varied by age group. For example, unintentional injuries were the leading cause for age group 1–44, accounting for 28.3% of all deaths for this age group.

The relative burden of mortality from various causes has changed over time. Two causes changed rank in 2014 compared with 2013. For example, Influenza and pneumonia moved down from eighth to 11th for males, while Alzheimer's disease moved up from ninth to eighth rank, and Influenza and pneumonia moved down from eighth to 11th for females.

Pubmed search results for “cardiotoxicity” & “chemotherapy”

- 1998 Herceptin approved in U.S.
- PubMed search results show an increase in publications related to cardiotoxicity and chemotherapy from 1965 to 2013.

Figure 2. Trends in Cardiovascular Medicine

Additional information on trends in cardiovascular medicine can be found in the Trends in Cardiovascular Medicine article cited in the figures.
All-cause mortality in adult cancer survivors who develop CVD

Patient AB
- 31 y/o F referred for consideration for an internal cardiac defibrillator (ICD)

**Oncologic History:**
- 1995 at age 11 diagnosed left distal femur osteogenic sarcoma with presumed pulmonary metastases
- Cisplatin, Doxorubicin, Methotrexate, macrophage stimulating factor MTP-PE as part of Children’s Cancer Group protocol
- 2 courses of induction chemotherapy followed by limb salvage surgery
- Resected bone tumor with <5% viable tumor, thoracotomy with no viable tumor in resected specimens

**ANTHRACYCLINES**

- Doxorubicin
- Epirubicin
- Daunorubicin
- Miloxantrone
- Idarubicin

Additional studies are needed to examine whether early screening and treatment of asymptomatic CVD may prevent the onset of cardiovascular disease (CVD) in cancer survivors. The current study speaks to the importance of strategies to improve cardiovascular health in at-risk survivors long after completion of cancer therapy.
Cardio-Oncology History

- During maintenance chemotherapy, fractional shortening on echo 26% (below lower limits of normal)
- Initiated on enalapril
- Last 2 courses of doxorubicin dropped from regimen, chemo completed 9/1996
- Total anthracycline dose = 300 mg/m²
- Followed at Children’s until 2006 & on digoxin, enalapril, lasix
- 2008 seen in Florida and desired pregnancy, cardiologist thought it was reasonable to stop all cardiac meds and follow
- 2009 in Kansas after birth of first child, told EF dropped by 10% & started on coreg, lasix
- Continued coreg and lasix through her second pregnancy and delivery 2014
- Came off cardiac meds to nurse and told week after delivery that EF 45-50%
- Plan to wait 6 months post-pregnancy to restart cardiac meds but at 4 months had echo which showed EF 20-25%
- Started on Lisinopril, metoprolol, spironolactone and told she would need an ICD and heart transplant soon

Case: AB (cont.)

- Vital signs: BP 98/58, HR 80
- Slow adjustments of heart failure meds using home BP monitoring
- Stable on metoprolol succinate 25 mg daily and enalapril 2.5 mg BID
- Cardiac rehab
- 2/2017 TTE – EF 50-55%

Cardiac events are dose dependent
Children’s Oncology Group
Recommendations

- Evaluation by a cardiologist for survivors who are pregnant or planning pregnancy and received:
  - Anthracycline ≥ 300 mg/m²
  - Radiation ≥ 30 Gy to the mediastinum
  - Radiation to the heart at any dose with anthracycline or high dose cyclophosphamide
- Suggested monitoring includes prior to and during pregnancy, especially 3rd trimester and cardiac monitoring during labor & delivery

Trastuzumab * Lapatinib * Pertuzumab * Ado-trastuzumab

HER 2 INHIBITION
Case: CD

- 38 y/o F with left breast invasive cancer, stage IIIA (T3N1M0), ER+/HER2+
- Lump discovered while breast-feeding her twins
- No significant PMH

Benefits of Herceptin

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
<th>Echo</th>
<th>SNP (0-100)</th>
<th>Trop (0-0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/2015-2/2016</td>
<td>Docetaxel/ Carboplatin/ Pertuzumab + Herceptin Q21 days x 12 mos</td>
<td>11/15 EF 62%</td>
<td>11/16 EF 68%</td>
<td></td>
</tr>
<tr>
<td>3/16</td>
<td>Herceptin</td>
<td>EF 57%</td>
<td></td>
<td></td>
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<tr>
<td>4/16</td>
<td>Herceptin, Bilateral mastectomy &amp; BSO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/2/16</td>
<td>Herceptin, L breast XRT, initiated ace I &amp; coreg</td>
<td>EF 47%</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>6/22/16</td>
<td>Herceptin held x 1 dose</td>
<td>EF 63%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/16</td>
<td>Herceptin</td>
<td>EF 56%</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>8/16</td>
<td>Herceptin</td>
<td>8/2 EF 55%</td>
<td>8/30 EF 60%</td>
<td>13</td>
</tr>
<tr>
<td>9/16</td>
<td>Herceptin</td>
<td>EF 55%</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>10/16</td>
<td>Herceptin</td>
<td>10/12 EF 60%</td>
<td>10/28 EF &gt;55%</td>
<td>17</td>
</tr>
</tbody>
</table>
FDA Guidelines

• Hold Herceptin
  – For at least 4 weeks if either:
    • ≥ 16% absolute LVEF decrease from baseline OR
    • LVEF < institutional limits of normal & ≥ 10%
      absolute LVEF decrease from baseline

• Resume
  – LVEF returns to normal limits in 4-8 weeks &
    absolute drop from baseline ≤ 15%

Kondapalli L. Cardiotoxicity: An unappreciated consequence of HER2-targeted therapies. In American College of Cardiology CardioSource. Late


ANDROGEN DEPRIVATION THERAPY

Leuprolide * Degarelix * Enzalutamide * Abiraterone acetate
Patient DE

- 80 y/o M COPD, current tobacco, HTN in the past, prostate cancer recently initiated on androgen-deprivation therapy (ADT) presents to discuss CV risk associated with treatment

**Oncologic History:**
- 1997 diagnosed with prostate cancer, PSA 6-8
- 1997 Radical prostatectomy
- Early 2000, PSA 0.5 then rose to 0.54 in 2009
- 2014 PSA 6.15
- Now on enzalutamide and leuprolide

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**AHA/ACS/AUA Advisory**

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Prospective Studies of the Effects of ADT on Cardiac Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column</td>
<td>Parameter</td>
</tr>
<tr>
<td>Quality</td>
<td>20-35</td>
</tr>
<tr>
<td>Serum lab</td>
<td>Baseline</td>
</tr>
<tr>
<td>HDL</td>
<td>Baseline</td>
</tr>
<tr>
<td>LDL</td>
<td>Baseline</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Baseline</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Baseline</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Baseline</td>
</tr>
<tr>
<td>Weight</td>
<td>Baseline</td>
</tr>
<tr>
<td>Height</td>
<td>Baseline</td>
</tr>
<tr>
<td>BMI</td>
<td>Baseline</td>
</tr>
</tbody>
</table>

- "There may be a relationship between ADT and CV risk."
- Advisable that patients in whom ADT is initiated be referred to their PMD for periodic follow up regarding lipid-lowering, antihypertensive, glucose-lowering and antiplatelet therapies

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**Table 3. ABCDE Algorithm for Prostate Cancer Survivors**

<table>
<thead>
<tr>
<th>A</th>
<th>Awareness</th>
<th>Increased awareness of patients of cardiovascular signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Blood pressure</td>
<td>Goal blood pressure &lt;140/90 mmHg</td>
</tr>
<tr>
<td>C</td>
<td>Cholesterol</td>
<td>High-intensity statin therapy for preexisting CVD or hyperlipidemia</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes mellitus</td>
<td>Frequent blood glucose monitoring</td>
</tr>
<tr>
<td>E</td>
<td>Exercise</td>
<td>150 min/wk of moderate-intensity physical activity or 75 min/wk of vigorous exercise</td>
</tr>
</tbody>
</table>

ABCD indicates cardiovascular disease.

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ANTHRYCLINE ANTIBIOTICS

- Mitoxantrone
- Idarubicin
- Epirubicin
- Daunorubicin
- Doxorubicin

Although Mitoxantrone technically belongs to the tumor antibiotics, it is related to the anthracycline family and is included here because of its cardiotoxic potential.

ANTHRACYCLINE ANTIBIOTICS (cont)

- Amsacrine
- Cyclophosphamide

ANTHRACYCLINE ANTIBIOTICS (cont)

- Doxorubicin
- Daunorubicin
- Epirubicin
- Idarubicin
- Mitoxantrone

ANTHRACYCLINE ANTIBIOTICS (cont)

- Doxorubicin
- Daunorubicin
- Epirubicin
- Idarubicin
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ANTHRACYCLINE ANTIBIOTICS (cont)

- Doxorubicin
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ANTHRACYCLINE ANTIBIOTICS (cont)

- Doxorubicin
- Daunorubicin
- Epirubicin
- Idarubicin
- Mitoxantrone
Rate of MACE increases with exposure to breast radiation (1958-2001)

![Graph showing the rate of MACE increases with exposure to breast radiation](https://example.com/graph)

- **Risk Factors**
  - Treatment Factors
    - Combined with radiation
    - Combined with other cardiotoxic therapy
      - Cyclophosphamide conditioning for IVCT
      - Anthracycline
  - Medical Conditions
    - Diabetes mellitus
    - Congestive heart failure
    - Hypertension
    - Hypothyroidism
    - Calcium channel blockers
  - Health Behaviors
    - Smoking
    - Drug use (e.g., cocaine, alcohol, marijuana)

- **Highest Risk Factors**
  - Female sex
  - Younger than age 5 years at time of treatment
  - Treatment Factors
    - Higher cumulative anthracycline dose
    - Total duration of anthracycline therapy
    - > 300 mg/m² in patients younger than 50 years at time of treatment
    - Any dose in adolescent
    - Chest radiation >10 Gy
    - Longer time elapsed

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Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

- Prevention and monitoring strategies should be tailored to the individual patient and should consider the patient's age, sex, and clinical status.

- Risk stratification should be based on the cumulative anthracycline dose, radiation therapy, and specific comorbidities.

- Routine surveillance with cardiac monitoring is recommended for certain higher risk survivors of cancer, including those who have received potentially cardiotoxic therapy.

- Follow-up imaging may be warranted after completion of cancer-directed therapy, so that appropriate interventions can be planned.

- Cardiac evaluation should be performed in any survivor who has received potentially cardiotoxic therapy and has symptoms or signs of cardiac dysfunction.

- The guideline recommendations were crafted in part using the Guidelines Into Decision Systematic Review (1996 to 2016) of meta-analyses, randomized clinical trials, observational studies, and consensus statements.

- The strength of the recommendations in these guidelines is based on the quality, consistency, and impact of the evidence and the balance between benefits and harms.

- Additional evidence tables, a methodological appendix, and comprehensive review and analyses of the relevant literature for each guideline are available at the ASCO website (www.asco.org).

- For more information, contact the American Society of Clinical Oncology, 2318 Mill Rd, Ste 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.
Who is at increased risk of developing cardiac dysfunction?

- Treatment that includes any of the following:
  - High-dose anthracycline
    - eg doxorubicin > 250 mg/m², epirubicin > 600 mg/m²
  - High-dose RT (> 30Gy) with heart in txmt field
  - Lower-dose anthracycline in combination with lower-dose RT (< 30Gy) with heart in txmt field

- Txmt with lower-dose anthracycline or trastuzumab alone with any of the following risk factors:
  - Multiple CV RF (> 2 RF): smoking, HTN, DM, dyslipidemia, obesity, during or after txmt
  - Older age (> 60 yrs) at cancer txmt
  - Compromised CV function before or during txmt
    - eg, LVEF 50-55%, h/o MI, > moderate valve dz

- Txmt with lower-dose anthracycline followed by trastuzumab (sequential therapy)

Evidence based
Evidence quality: intermediate
Benefits outweigh harms
Strength of recommendation: moderate
**Which preventative strategies minimize risk before starting txmt?**

- **Recommendation:**
  - Avoid or minimize use of potentially cardiotoxic txmt if established alternatives exist that would not compromise cancer-specific outcomes

<table>
<thead>
<tr>
<th>Consensus based</th>
<th>Benefits outweigh harms</th>
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<tbody>
<tr>
<td>Strength of recommendation: strong</td>
<td></td>
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</table>

**Which preventative strategies minimize risk before starting txmt?**

- **Recommendation:**
  - Clinicians should perform a comprehensive assessment of patients with cancer including H&P, screening for CV risk factors and echo prior to starting potentially cardiotoxic txmt

<table>
<thead>
<tr>
<th>Evidence and consensus based</th>
<th>Benefits outweigh harms</th>
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</thead>
<tbody>
<tr>
<td>Evidence quality: high</td>
<td>Strength of recommendation: strong</td>
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</table>

**Which preventative strategies minimize risk during txmt?**

- **Screen for and manage modifiable CV RF**

<table>
<thead>
<tr>
<th>Informal consensus &amp; evidence based</th>
<th>Benefits outweigh harms</th>
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</thead>
<tbody>
<tr>
<td>Evidence quality: insufficient</td>
<td>Strength of recommendation: moderate</td>
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</table>

- **Incorporate strategies in patients receiving high-dose anthracycline**
  - Cardioprotectant dexrazoxane
  - Continuous infusion or liposomal doxorubicin

<table>
<thead>
<tr>
<th>Evidence based</th>
<th>Benefits outweigh harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence quality: intermediate</td>
<td>Strength of recommendation: moderate</td>
</tr>
</tbody>
</table>
What is the preferred monitoring approach during txmt?

• Careful H&PE
• In patients with signs or sx of cardiac dysfunction the following:
  – Echo for dx workup
  – MRI or MUGA if echo not adequate (MRI preferred)
  – Cardiac biomarkers or strain in conjunction with routine diagnostic imaging
  – Referral to cardiology based on findings

• Routine surveillance imaging may be offered in asymptomatic patients at increased risk
  – Echo is modality of choice

• No recommendation regarding continuation or discontinuation of cancer txmt

What is the preferred monitoring approach during txmt?

• Routine echo surveillance may be used in patients with metastatic breast cancer receiving trastuzumab indefinitely
What is preferred monitoring after txmt in patients at risk?

- Careful H&PE in survivors
- Pts with signs, sx of cardiac dysfxn should undergo diagnostic eval

What is preferred monitoring after txmt in patients at risk?

- Echo* may be done 6-12 months after cancer txmt in asymptomatic pts at increased risk of cardiac dysfxn
- Pts with asymptomatic cardiac dysfxn should be referred to cardiology
- Regularly eval and manage cardiac RF
- No recommendation for pts at increased risk with normal echo and eval at 6-12 mos

Summary

- Cardio-oncology is an area of cardiology focused on managing acute and long-term side effects of cancer therapy
- Anthracyclines and trastuzumab can cause cardiomyopathies which can respond to standard heart failure therapy
- Patients with prostate cancer on androgen deprivation therapy may benefit from aggressive cardiac risk factor modification
- COG and ASCO guidelines can help in managing these complex patients
Thank you!

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