Cardio-oncology: A practical overview for the cardiologist

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Learner Objectives
• Epidemiology of cardio-oncology
• Understand risk factors for cardiotoxicity
• Identify manifestations of cardiotoxicity by different cancer treatment modalities, focusing on the 3 most common offending agents
• Screening for cardiotoxicity
• Prevention and treatment of cardiotoxicity

Case 1
• 61 yo woman w/ metastatic renal cell carcinoma starting sunitinib. What is most common complication?
1. CHF
2. Bradycardia
3. Hypertension
4. Coronary thrombosis

(Biar SM Mosleh J 2013)
Case 2

- 48 year old woman with HER2+ breast cancer, s/p lumpectomy, receiving adjuvant chemotherapy and trastuzumab. 12 weeks into treatment, EF drops from 56% at baseline to 33%. No HF sx.
- BP 130/87, HR 77. RRR no m/r/g. No JVD or edema.
- What do you do?

1. Cont. w/ treatment – cancer will progress otherwise. Repeat echo in 1 month.
2. Start carvedilol, lisinopril, continue with treatment.
3. Prescribe a Life Vest for primary prevention of SCD.
4. Hold chemo; start ACEI/BB, repeat echo in 4 weeks.

(Blair SM Mosleh J 2013)

What is cardio-oncology?

- Cardiac subspecialty focusing on the screening, evaluation, prevention, and treatment of CV complications during or after cancer therapy
- Cancer treatments are progressing rapidly – more drugs being developed for cancer than any other condition—cardiologists must keep up and provide recommendations tailored to each patient and their cancer treatment plan

Rapid pace of change

The big 6

- Drugs in development
- Phase I/II
- Phase III
- Phase IV
- Marketed
- Out of field

Cancer

- Cancer stem cells
- Metastasis
- Inflammation
- Pain and discomfort
- Functional status
- Quality of life
- Genetic alterations
- Psychosocial
- Economic

“This is our moonshot...to end cancer as we know it.”

One of the 10 recommendations for the 2016 Cancer Moonshot initiative

Minimize cancer treatment’s debilitating side effects...This recommendation calls for research to support development of guidelines for managing patient-reported symptoms and side effects of cancer treatment in adults and children, with the goal of helping patients stay on their drug regimens and improve their quality of life.
What’s the connection?

• In childhood cancer survivors, CV mortality is 5-fold higher than general population.
• HF patients with cancer have 5% increased mortality.
• Cancer treatment accelerates the development of CV disease.
• RF’s overlap: obesity, tobacco, age, inflammation, poor nutrition.
• Like HIV and other diseases, cancer is often a chronic condition and patients may live to suffer from heart disease.
• CV health is essential for good cancer treatment outcomes.

Types of CV complications and toxicities from cancer treatment

• Arrhythmia.
• Myocyte necrosis → dilated cardiomyopathy (DCM).
• Vascular: VTE, ATE, vasospasm, accelerated atherosclerosis → angina, MI.
• Hypertension.

Cancer timeline

1963 1st anthracycline discovered
1966 cardiotoxicity reported from daunorubicin
1977 dose dependent identified
1983 Gleevec (imatinib) revolutionizes treatment of CML and kickstarts the development of targeted therapies.
2007 TK/multikinase inhibitors found to cause HTN, HF, ATE, VTE.

Anthracyclines

• CHF developed with maintenance treatment.
• Dose dependent (>300-400 mg/m²).
• 30% of children had cardiac dysfunction at long-term follow-up.
• Anthracyclines block topoisomerase II to prevent DNA replication. Why should that affect terminally differentiated cardiac myocytes?
Anthracyclines
- Anthracyclines generate toxic hydroxyl radicals
- They bind to promoters that regular gene transcription and block them
- Acute toxicity: uncommon
  - SVT, VT, heart block, acute LV dysfxn
- Subacute
  - Esp. with CHOP treatment of lymphoma in elderly patients
  - A fib, LV dysfunction, HF, Ischemia
- Chronic
  - Asymptomatic LV dysfunction → clinical HF
  - Can present in first year, in first 5 years, and even late (>10 yrs)
  - Risk factors: cumulative dose (usu >400 mg/m²), age, concomitant trastuzumab (Herceptin), XRT, pre-existing CV disease (CAD, HTN, DM, PAD)

Trastuzumab
- Treatment of metastatic ERBB2 (HER2)-positive breast cancer
- ERBB2 belongs to the family of human epidermal growth factor receptors (EGFRs). Trastuzumab inhibits the dimerization of ERBB2/ERBB3
- However, ERBB2 is also expressed on cardiomyocytes, and deletion of it causes DCM

Trastuzumab, the revolution in breast cancer chemotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>NYHA II or IV Heart Failure incidence</th>
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</thead>
<tbody>
<tr>
<td>Anthracycline + cyclophosphamide + trastuzumab</td>
<td>27%</td>
</tr>
<tr>
<td>Anthracycline or cyclophosphamide alone</td>
<td>8%</td>
</tr>
<tr>
<td>Paclitaxel + trastuzumab</td>
<td>13%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>1%</td>
</tr>
</tbody>
</table>

- Toxicity is synergistic with anthracyclines
- Cardiotoxic on its own
- Not dose dependent
- Often reversible with cessation of therapy
- Rechallenge is often well tolerated
- Pertuzumab (Perjeta) targets a different domain often added for synergy/resistance; well tolerated without cardiotoxicity

Aromatase inhibitors
- Used for ER+ and/or PR+ breast cancer
- Block aromatase which turns androgens into estrogens
- Oral daily medications, taken for years to suppress cancer recurrence
  - Arimidex (anastrozole)
  - Aromasin (exemestane)
  - Femara (letrozole)
- Cardiotoxicity: vasodilation, edema, endothelial dysfunction, angina/worsening of ischemic heart disease
UCSF breast cancer echo protocol

- For trastuzumab – obtain baseline echo and echo q 3 mo until completion of trastuzumab
- For doxorubicin alternating w/ HER2 agents, then obtain baseline echo and prior to switching from anthracycline to HER2 targeted agent.
- If 10% drop in EF and asymptomatic → hold agent x 4 wks, repeat echo.
- If EF improves, consider resuming chemo, consider referral to cardiology.
- If EF drop is significant, HF sx, refer to cardiology.

Treatment of anthracycline or trastuzumab toxicity

- Cease the use of anthracyclines
- Treat with ACEI, carvedilol/BB
- Reassess LVEF in 4 weeks
- Rechallenge with trastuzumab once EF normalizes (>50%)


Can cardiomyopathy be predicted?

- Holding chemo for 4 weeks and being told you have cardiac dysfunction when you are already dealing with a cancer diagnosis can be frightening.
- Are there ways to identify at-risk patients earlier, and intervene?

The role of strain imaging

- Strain = dimensionless parameter. Change in length of myocardial segment compared to its baseline length, expressed as a percentage. Strain rate = Rate at which myocardial deformation takes place. 1s. Less influenced by loading conditions, less influenced by global function, thus a more sensitive assessment of true regional function.
- Helps detect more subtle myocardial problems.

The role of strain imaging

**Speckle tracking**

**Pitfalls:**
- VERY dependent on 2D image quality
- Interobserver and intraobserver variability / reproducibility

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**Strain to detect cardiotoxicity**

- Can you identify the ACC/AHA Stage A patient ("at risk" for HF but without overt LV dysfunction) using strain imaging?
- Relative change in strain by 10-15% compared to prior study is the most useful parameter for predicting cardiotoxicity from chemotherapy.

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**Cardio-oncology echo pearls**

- Carefully measure LVEF esp. if EF has dropped >10 points from last echo
- Beware of the borderline or low-normal EF
- Use contrast if needed
- Consider taking into account strain imaging
- Keep mind of strain imaging limitations
Other markers

- Mixed results on whether troponin can predict cardiotoxicity
- Pro-BNP did not predict cardiotoxicity
- Cardiac MRI and molecular imaging may be helpful in the future to detect subclinical cell death
- ERNA (MUGA)

Tyrosine kinase inhibitors – a major advance in designer drugs…with CV costs

- The pre- and post-Gleevec era
- A magic bullet to cure CML, a once-fatal disease
- “Gleevec opened a new door for cancer therapeutics. The rational synthesis of a molecule to kill cancer cells – a drug designed to specifically inactivate an oncogene…”
- Some tyrosine kinase inhibitors (TKIs) have specific targets and others target multiple kinases. Off-target effects → off-target side effects

Tyrosine kinase inhibitors – a major advance in designer drugs…with CV costs

- The “—ib’s”
- Sunitinib – multikinase inhibitor - treatment for RCC
- Inhibit angiogenesis and cell growth (affect VEGF, fibroblast growth factor receptors, and platelet-derived growth factor receptors (PDGFRs))
- Hypertension (systolic and diastolic)
- QT prolongation (dasatinib, nilotinib)
- Pulmonary hypertension (nilotinib, dasatinib)
- Atherosclerosis
- Arterial and venous thromboembolism
- …sometimes leading to heart failure (esp. imatinib)
VEGF signaling pathway inhibitors

- Another bench to bedside breakthrough: Reduce cancer angiogenesis
- Hypertension almost universal
- Dose-dependent, often transient, within a week
- Incidence 20-25% with bevacizumab (Avastin) and up to 50% with sunitinib
- Treatment with ACEI, calcium channel blockers often effective
- Uncommon to have to discontinue the chemo agent for HTN

Fluoropyrimidines (5FU, capecitabine)

- 3rd most commonly used chemotherapeutic for solid tumors
- GI, breast, head and neck
- Cardiotoxicity uncommon but be aware (<10%)
- Angina, MI, HF, pericarditis, myopericarditis
- Idiosyncratic
- Avoid repeat administration

Case 3

- 51 y/o previously healthy, fit patient who had an uncomplicated partial colectomy for sigmoid colon cancer on 8/18/15. He started FOLFOX for stage III colon cancer and developed chest pain during his first 5FU infusion. EKG changes were noted.
Patient now on surveillance alone after 2 cycles of adjuvant FOLFOX. No radiographic evidence of recurrent or metastatic disease on current CT scan. Followed in GI Onc Survivorship Clinic.

### Fluoropyrimidines (5FU, capecitabine)
- Chest pain may be due to coronary spasm
- Usually reversible, usually IS recurrent if re-administered
- Risk factors: preexisting CAD, older age
- Treatment: nitrates, calcium channel blockers, revascularization
- Avoid premature/unnecessary cessation as that may affect cancer curability
  - Screening treadmill may not be sufficient
  - Think about coronary CT angio, cath

### Types of complications and toxicities from fluorouracil
- Arrhythmia
- Myocyte necrosis → dilated cardiomyopathy (DCM)
- Vascular: VTE, ATE, vasospasm, accelerated atherosclerosis → angina, MI
- Hypertension
- Valvular disease
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Future directions - immunotherapy

PD-1 checkpoint inhibitors:
- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)

Autoimmune myocarditis with cancer immunotherapy

PD-1 checkpoint inhibitors: Pembrolizumab (Keytruda), Nivolumab (Opdivo)
Summary

• Anthracyclines – DCM, early and late
• Trastuzumab – DCM, usually when on treatment
• EF drop >10 points or to <50%; stop; treat HF; repeat echo; consider resuming chemo. Consider using strain imaging
• TK inhibitors – optimize pts with pre-existing CAD, HTN
• VEGF signaling pathway inhibitors – Treatment related HTN
• Fluorouracils – optimize pts with pre-existing CAD, HTN; think about vasospasm
• Stay abreast of newer agents
• Work as a team with oncologist to see how to optimize cardiac status to facilitate continued cancer treatment