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

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Learning Objectives

• Introduce the field of cardio-oncology, a new subspecialty within cardiology
• Identify cardiovascular disease as a leading cause of death in cancer survivors
• Discuss the management of cardio-oncology issues within the context of case presentations
Management of cardiac conditions in patients undergoing cancer treatment and in cancer survivors

CARDIO-ONCOLOGY

PubMed “cardiotoxicity” & “chemotherapy”

1973 Lefrak et al. report HF with doxorubicin
1998 trastuzumab approved in U.S.

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

All-cause mortality in adult cancer survivors who develop CVD


ANDROGEN DEPRIVATION THERAPY

Leuprolide * Degarelix * Enzalutamide * Abiraterone acetate
Patient AB

- 79 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

**AHA/ACS/AUA Advisory**

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

Table 3. ABCDE Algorithm for Prostate Cancer Survivors

| A | Awareness | Increased awareness of patients of cardiovascular signs and symptoms |
| B | Blood pressure | Goal blood pressure <140/90 mm Hg |
| C | Cholesterol | High-intensity statin therapy for preexisting CVD or hyperlipidemia |
| C | Cigarettes | Smoking cessation counseling, therapy |
| D | Diabetes mellitus | Frequent blood glucose monitoring |
| D | Diet | Metformin for diabetes mellitus if possible |
| D | Diet | Diet rich in fruits, vegetables, and whole grain and low in saturated fat with 600 IU vitamin D daily and adequate calcium (1200 mg/d) |
| D | Avoidance of excessive alcohol | Avoidance of excessive alcohol |
| E | Exercise | 150 min/wk of moderate-intensity physical activity or 75 min/wk of vigorous exercise |

CVD indicates cardiovascular disease.


Patient AB (cont.)

- Vitals: 135/86, HR 78, 98% RA, BMI 25
- Chol 151, LDL 72, HDL 59, trig 99
  - 10-year ASCVD risk 30.7%*
  - Framingham risk score = 17.5%
- HgB A1c 6.2%
Patient AB Recommendations

• Moderate to high intensity statin
• Aspirin 81 mg daily
• Diet modification being mindful of salt and sugar intake
• Exercise
• Tobacco cessation

ANTHRACYCLINES

- Doxorubicin
- Epirubicin
- Daunorubicin
- Mitoxantrone
- Idarubicin
Patient CD

- 72 y/o M amyotrophic dermatomyositis and calcinosis cutis, moderate aortic stenosis, PAD, DM, HTN, HLD, CAD s/p NSTEMI 2/2016, GIB with newly diagnosed non-Hodgkin’s lymphoma

- Plan for anthracycline-based chemotherapy (RCHOP)

Cardiac events are dose dependent
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
Rate of MACE increases with exposure to breast radiation (1958-2001)


Who is at increased risk of developing cardiac dysfunction?

- 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
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>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence quality: high</td>
<td>Strength of recommendation: strong</td>
</tr>
</tbody>
</table>

Patient CD

- 72 y/o M amyotrophic dermatomyositis and calcinosis cutis, moderate aortic stenosis, PAD, DM, HTN, HLD, CAD s/p NSTEMI 2/2016, GIB with newly diagnosed non-Hodgkin’s lymphoma
- Plan for anthracycline-based chemotherapy (RCHOP)
Pt CD: Pre-txmt

- Dobutamine stress echocardiogram performed to assess aortic valve gradients:
  - Normal resting LV size and systolic function. There are no resting wall motion abnormalities noted.
  - Appropriate increase in LV function with IV dobutamine. There are no inducible regional wall motion abnormalities noted.
  - At rest, there is moderate aortic stenosis with a mean gradient across the valve of 34 mm Hg, a calculated AVA of 1.2 cm², and a dimensionless index of 0.30.
  - With dobutamine infusion (10 mcg/kg/min), the mean gradient goes to 41 mm Hg with a peak velocity across the valve of 4.6 m/sec.
  - No ECG evidence of ischemia.

Which preventative strategies minimize risk during txmt?

- Screen for and manage modifiable CV RF
  - Informal consensus & evidence based
  - Benefits outweigh harms
  - Evidence quality: insufficient
  - Strength of recommendation: moderate

- Incorporate strategies in patients receiving high-dose anthracycline
  - Cardioprotectant dexrazoxane
  - Continuous infusion or liposomal doxorubicin
  - Evidence based
  - Benefits outweigh harms
  - Evidence quality: intermediate
  - Strength of recommendation: moderate
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

What is the preferred monitoring approach during txmt?

- 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
Patient CD: During txmt

- Discussed with oncologist
- Expected volume 1.3 L which may be less after first infusion
- Infusion Adriamycin more volume than bolus
- Recommendations:
  - Lasix IV after infusion
  - Admission for administration of first cycle and observation overnight. Keep on telemetry.
  - Immediate cardiology consult if any concern for heart failure symptoms.

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

Patient CD: Post-txmt

- Completed mini-RCHOP x 6 cycles
- Cycles 2-6 outpatient

- Unfortunately developed non-healing foot ulcer 2/2 PAD, unable to revascularize percutaneously and awaiting amputation
Patient EF

- 68 y/o F with newly diagnosed metastatic renal cell carcinoma
  - 2007 Diagnosed with renal cell carcinoma
  - Treated with nephrectomy
  - Imaging at 5 years (2012) revealed no recurrence
  - No subsequent follow up

- Summer 2014 acute onset shortness of breath and back pain which led to diagnosis of metastatic renal cell carcinoma
Patient EF (cont.)

• She was also diagnosed with new systolic heart failure

• EF 30%

Should the patient receive pazopanib (Votrient)?
**Cardiac Side Effects of VSP Inhibitors**

- HTN is the most common cardiac toxicity in every trial

- Other side effects:
  - arterial and venous clots
  - cardiomyopathy

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**Table 3: Cautions, contraindications, and compelling considerations for major classes of antihypertensive drugs**

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Cancer-specific cautions or reasons to avoid</th>
<th>Basis for preferred selection</th>
<th>General cautions and contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Coadministration titration with renal clearance-dependent agents (e.g., captopril, perindopril) hypertensive</td>
<td>Left ventricular systolic dysfunction, diabetic nephropathy</td>
<td>Renovascular disease, peripheral vascular disease, renal impairment</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>Coadministration titration with renal clearance-dependent agents (e.g., enalapril, perindopril) hypertensive</td>
<td>Intolerance of other agents, especially ACE inhibitors, left ventricular systolic dysfunction, diabetic nephropathy</td>
<td>Renovascular disease, peripheral vascular disease, renal impairment</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Asthenia, malaise, fatigue, QT interval prolonging drugs</td>
<td>Angina, history of myocardial infarction, anxiety</td>
<td>Bradycardia, heart block, diabetes (risk for hypoglycemia), asthma, chronic obstructive pulmonary disease (wheezing), decompensated heart failure</td>
</tr>
<tr>
<td>Calcium channel blockers (e.g., diltiazem, verapamil)</td>
<td>Lower extremity swelling, Gout, hypercalcemia, hypokalemia, young patients (age ≤45 yrs), QT interval prolonging drugs</td>
<td>Elderly patients, isolated systolic hypertension, secondary stroke prevention, typically least expensive</td>
<td>Preexisting edema, slow onset of action, Gout, documented sulfa allergy</td>
</tr>
</tbody>
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Patient EF

- Significant hypertension with pazopanib
- Added metoprolol, ace inhibitor, aldactone, lasix and had to dose reduce pazopanib 2/2 BP
- Has stable disease with pazopanib

TYROSINE KINASE INHIBITORS

Ibrutinib * Everolimus * Dasatinib * Nilotinib * Ponatinib * Crizotinib
Patient GH

- 65 y/o M with CLL diagnosed in 2010
- 6/2015 Started ibrutinib
- 1/2016 New heart racing
- 2/2016 Admission for neutropenia, rhinovirus, afib started on rate control
- 4/5/16 ECG – afib at 112 bpm

Ibrutinib

- Systematic review and pooled analysis of 4 RCTs showed compared to controls, ibrutinib was associated with:
  - Significantly higher incidence of afib/flutter
  - Higher incidence of all-grade bleeding
- Currently no consensus on best anticoagulation strategy

Patient GH

- Initial visit: resume ibrutinib, apixaban, up-titrate rate control
- Subsequent echo showed EF 45-50% (baseline EF normal)
- DCCV + tikoosyn
- Recent EF 60%

Summary

- Cardio-oncology is an area of cardiology focused on managing acute and long-term side effects of cancer therapy
- Prostate cancer patients on ADT may benefit from aggressive cardiac risk factor modification
- ASCO guidelines can help gauge risk
- VEGF inhibitor therapy can cause hypertension
- Ibrutinib can cause atrial fibrillation and increase bleeding risk
All-cause mortality in adult cancer survivors who develop CVD


Thank you!

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