CARDIOVASCULAR COMPLICATIONS OF CANCER TREATMENT

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Memorial Sloan-Kettering Cancer Center
Education:
Residents and Clinical Fellows 1,682

Staff:
Total Staff 12,402
Volunteers 1,018

Patient Care:
Patient Admissions: Adults 23,139
Patient Admissions: Children 1,459
Total Admissions 24,598
Beds in Service 469
Total Outpatient Services 541,474
Surgical Cases 19,6910
Cardiology at MSKCC

- 10 full time cardiologists
- 3000 inpatient consultations and 3000 longitudinal clinic visits/yr
- MPI, CTA, CMR, TTE, TEE
- CICU- 8 beds
- 8 telemetry beds
- 9 MLPS
- 2 Fellows
Traditional View

CVD

CA
Cancer Treatment

CVD and CA intersection

- HTN
- Accelerated atherosclerosis
- Endothelial dysfunction
- Primary electrical effects pro-arrhythmogenic
- Valvular heart disease
- Direct myocardial toxicity
- Pericardial disease
- Impact of CVD during CA treatment
- LV dysfunction CHF
Realities

CVD

CA
CVD consequences of cancer care

Some immediate and some long term effects

• GU cancer
• Breast cancer
• Colorectal ca
• Lung ca
• Multiple myeloma
• Lymphoma /leukemia
• sarcoma
Late effects of cancer survivors: the scope of the problem

- More than 10 million cancer survivors in US in 2002
- Magnitude of population at risk for CVD sequelae is growing, given growing number of cancer survivors
Cardiovascular Complications of Radiation Therapy
Case: XRT

• 48 year old woman, Hodgkin's in her 20’s, treated with CHOP, mantle and para-aortic XRT

• H/o obesity. No cardiac symptoms. No HTN/NIDDM/cig/ FH.

Being evaluated for possible bariatric surgery. Referred for stress test.
Radiation Treatment

• Affects every component of the heart
• Often sub-clinical, about 10% symptomatic
• 50% asymptomatic pts develop new perfusion defects on nuclear imaging
• Historically most common presentation—early pericardial effusion
• Late constrictive pericarditis 5-10 yrs
• Marked improvement w newer shielding
Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

- RT to the heart during breast cancer Rx increases subsequent rate of ischemic heart disease. Increase is proportional to mean dose to the heart, begins within a first 5 yrs after exposure, and continues for at least 20 years.
- Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray. Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy than other women. - Darby et al, N Engl J Med 2013
Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Increase per gray, 7.4% (95% CI, 2.9–14.5)  
P<0.001
Baroreflex Failure

- Chronic inflammation and fibrosis of carotid arterial walls lead to splitting of carotid sinus baroreceptors
- Autonomic dysfunction- labile BP and orthostatic intolerance
- Labile BP can vary from acute onset of HTN crisis to a chronically volatile BP, tachycardia, headache
- Progressive, late after RT as pts age
Unanswered Questions

• Screening pre treatment?

• Surveillance post treatment- when, how, in and by whom?

• Early, aggressive risk factor modification- high risk group with different treatment goals for CVD risk factors?
Cardiovascular Complications of Chemotherapy

And newer targeted agents
Risk Factors for Developing CV Complications

- Multifactorial
- Dose delivered each session
- Cumulative dose
- Route of administration
- Combination of drugs given
- Sequence of administration
- RT – previous or concomitant
- Pt related risk factors- age, previous CVD, HTN, CM
Cardiotoxic Syndromes Associated With Chemotherapeutic Agents

- **Agents associated with myocardial depression:**
  - Anthracyclines
  - Mitoxantrone (Novantrone)
  - Cyclophosphamide (Cytoxan) high dose
  - Trastuzumab (Herceptin)
  - Ifosfamide (Ifex)
  - All-trans retinoic acid (Tretinoin)

- **Agents associated with ischemia:**
  - 5-FU (Adrucil)
  - Cisplatin (Platinol)
  - Capecitabine (Xeloda)
  - IL-2

Yeh, E. et al Circ 2004;109:3122-3131
Cardiotoxic Syndromes Associated With Chemotherapeutic Agents

• Agents associated with hypotension:
  Etoposide (Vepesid)  Paclitaxel (Taxol)  
  Alemtuzumab (Campath)  Cetuximab (Erbitux)  
  Rituximab (Rituxan)  IL-2  
  Denileukin (Ontak)  Interferon-a  
  All-trans retinoic acid (Tretinoin)

• Agents associated with hypertension:
  Bevacizumab (Avastin)  
  Cisplatin (Platinol)
Cardiotoxic Syndromes Associated With Chemotherapeutic Agents

- **Agents associated with other toxic effects:**
  - Cardiac tamponade or endomyocardial fibrosis: busulfan (Myleran)
  - Hemorrhagic myocarditis: cyclophosphamide (Cytoxan)
  - Bradyarrhythmias: paclitaxel (Taxol), thalidomide (Thalomid)
  - Raynaud phenomenon: vinblastine (Velban)
  - Late onset CAD: cisplatin
  - Venous thrombosis: Platin agents
  - Autonomic neuropathy: vincristine (Oncovin)
  - QT prolongation or torsades de pointes: arsenic trioxide
  - Pulmonary fibrosis: bleomycin (Blenoxane)
Anthracyclines

Doxorubicin, daunorubicin, idarubicin, epirubicin
Case: Adriamycin/Doxorubicin

- 68 year old woman with breast cancer, no cardiac risk factors, h/o obesity
- Mastectomy 12/2006, 1/17 + nodes
- ACT -> Adriamycin 240mg/m-sq with cyclophosphamide, followed by Paclitaxel
- Completed 6/2007
- 10/2007 Admitted with fever, dyspnea, ruled out for PE and treated for cellulitis
- 11/2007 Admitted with dyspnea
Cardiotoxicity of Anthracyclines

- Cardiomyopathy - dose dependent progressive decline in systolic function, ultimately -> restrictive pattern
- 30% incidence of CHF with >550mg/m2
- Historically more than ½ all pts exposed to AC -> some degree dysfunction 10-20 yrs
- Rare acute myopericarditis - stress induced CM
Cumulative probability of developing doxorubicin-induced congestive heart failure (CHF) plotted against total cumulative dose of doxorubicin in all patients receiving the drug (3941 patients; 88 cases of congestive heart failure)
Risk Factors for AC Cardiomyopathy

- Pre-existing HTN, coronary artery disease, LV dysfunction, NIDDM
- Age > 60 yrs, age < 18 yrs
- Dose of > 300mg/m2 of Doxorubicin
- Mediastinal radiation
- Combination chemotherapy
- Increased survival time
- Black pts at higher risk
Cellular Changes w AC Cardiotoxicity

Toxicity

• Early onset (<1 yr) and late onset (> 1 yr) cardiotoxicity
• Late cardiotoxicity assoc predominantly with fibrosis
• ? insidious course - latency may be subclinical dz slowly progressive over time - subclinical findings, troponin leaks etc
• Increase in TNI soon after HDC is a predictor of LV dysfn and poor cardiac outcomes, esp w persistent release- Cardinale JACC 2000
• Multiple hit hypothesis- ventricles more susceptible to other insults e.g. HTN, ischemia, sepsis
• Autopsy reports show intracellular deposits of hydroxylated AC- perhaps poison pill
Prevention

• Schedule modification- decreasing peak dose by increasing infusion time, pegylated preparations
• Some studies suggest use of analogues such as epirubicin, idarubicin
• Cardioprotective agents – mitoxantrone, dexrazoxane
• Intense monitoring- biomarkers and imaging
• Prophylaxis:
  ACE inhibitors in adults w increase in troponin I soon after exposure to high dose AC- prevented development of CM at 1 yr - Cardinale Circ 2006
  Carvedilol suggested by one small study – Kalay JACC 2006
  Statins used uninterruptedly assoc w lower incidence of CHF- Seicean JACC 2012
Case: oral 5 FU- Capecitabine

- 38 y/o h/o hyperlipidemia, nonsmoker, no HTN/NIDDM, receiving treatment for colon cancer. Good functional capacity.
- Started on Capecitabine (Xeloda) 3500mg QD.
- Few days later new onset DOE, palpitations w mild exertion, unable to tolerate her usual work out.
- Stress test was performed
Stress test on Xeloda

09/25/2007 11:15 AM
Rest LAX
HR 52 BPM

09/25/2007 11:15 AM
Impost LAX
HR 151 BPM
T01 00:00:52

Rest

Stress
5-Fluorouracil

2\textsuperscript{nd} most common cause of chemo cardiotoxicity

Occurs in < 2 \%, more common w/in 72hrs of 1\textsuperscript{st} cycle

- Precordial pain- angina and non-specific CP
- ST-T wave changes
- Acute myocardial infarction
- Atrial and ventricular arrhythmias
- Ventricular dysfunction- cardiac failure, pulmonary edema, cardiogenic shock- stunned myocardium
- Those who developed cardiac toxicity and recovered usually redeveloped it when re-challenged with drug
- Increased likelihood of events with pre-existing CAD
5FU cardiotoxicity

• Mechanism commonly held to be vasospasm
  – 30 patients exposed to 5FU vs. 30 controls non-5FU chemo
  – Brachial artery diameter pre- and post- chemo
  – Significant decrease in brachial artery diameter in 50% of patients exposed to 5FU, no change in control group
  – 86% of patients demonstrated reproducible vasospasm with 5FU (Ann Oncol 2004:12(5);723-724)

Mixed response to treatment with calcium channel blocking agents and nitrates leaves unanswered questions ab mechanism
Case: Cisplat

• 21 y/o man with germ cell tumor, presented after his first round of etoposide and cisplatin

• No h/o HTN, hyperlipidemia, NIDDM or family h/o CAD. Occasional marijuana use. Presents to ED with chest pain
NORMAL SINUS RHYTHM

ST ELEVATION CONSIDER INFARCTION OR ACUTE INFARCTION

ACUTE MI

ABNORMAL ECG

WHEN COMPARED WITH ECG OF 08-APR-2011 15:21,
ST ELEVATION NOW PRESENT IN INFERIOR LEADS
ST NOW DEPRESSED IN ANTEROLATERAL LEADS
T WAVE INVERSION NOW EVIDENT IN ANTEROLATERAL LEADS

CALLED UCC 9:40 AM, DR. CUTZU AWARE...
Cisplatin

- Used to treat germ cell tumors-highly curable >90% 5yr survival rate
- Best known for nephrotoxicity
- Acute CV effects- SVT, bradycardia, ST-T wave abnl, acute ischemic events
- Vascular toxicities- Raynaud’s phenomenon, HTN, cerebral ischemic events
Cisplatin: Potential Pathophysiology

• Underlying mechanism under investigation – measure CIMT and vWF before cisplatin and after, 65 patients, median age 27 (JCO 2008;23(12):9130-6)
  – Two acute myocardial infarctions, both smokers and obese, one with occluded RCA, other with normal coronaries
  – Found CIMT increased faster than expected for age-matched controls
  – Higher vWF, suggests endothelial damage
• May explain increased CAD recently identified in testicular cancer survivors – 5 year f/u in 2152 patients noted 1.9 fold increase in MI compared to controls (JCO 2006;24(3):467-75)
Germ Cell Tumor Survivors

Increasing evidence of long term increase in vascular toxicity

- 7-fold increase in ischemia at 10yrs - Meinardi
- Chemo regimen makes difference - Vanden Belt
- Increased risk of HTN, hyperlipidemia, plasma renin and aldosterone
- Troponin I elevation after high dose platinum derivatives predicts late cardiac dysfunction and major cardiac events - Cardinale
Tyrosine Kinase-Targeting Drugs

TKIs
Tyrosine Kinases

- Catalyze transfer of phosphate from ATP to tyrosine
- Regulate cell proliferation, survival, differentiation, function, motility
- TK dysregulated in cancer cells- felt to be implicated in 70% of malignant transformation-opportunity for targeted cancer therapy
- Significant impact:
  metastatic breast cancer ErbB2 + addition to standard chemo leads to 20% decrease in death at 1 yr
  90% CML Phila + treated alive at 5 yrs- previously uniformly fatal
- Anticipate increasing applications in hematologic disorders and solid tumors– large no. on horizon- approx 10,000 in development
Tyrosine kinase-targeting drugs with known cardiac toxicity

- Trastuzumab (Herceptin)- LV dysfn, CHF
- Bevacizumab (Avastin)- HTN, CHF
- Sunitinib (Sutent)- HTN, CHF, arterial thrombosis
- Imatinib (Gleevec)- CHF, pericardial effusion
- Dasatinib (Sprycel)- CHF, edema
- Nilotinib (Tasigna)- QT prolongation
- Sorafenib (Nexavar)- ACS, HTN, CHF
Trastuzumab - Herceptin

- Monoclonal Ab binds to ErbB2 receptor-extracellular domain of HER2 protein
- 20-25% of breast Ca over-express human epidermal growth factor receptor (HER2)
- Indicated in combination with Paclitaxel for adjuvant 1st line rx; single agent for second or third line rx.
- 1st line rx: Improves response rate, time to progression, time to treatment failure and median overall survival.
- Used for localized and metastatic dz
Trastuzumab Toxicity

- Cardiomyopathy
- Mechanism- ErbB2 receptor blocked by Tz, is needed for neuroreglin pathway. Neuroreglin thought to play impt role in myocyte survival during myocardial stress.
- Differs from AC toxicity in that it is not dose dependent
- Risks -advanced age, AC treatment, marginal or low EF after chemotherapy
- Increases susceptibility to AC toxicity
Tz Cardiomyopathy

- Initial rates were high when AC and Tz given concurrently – done in MBC
- Subsequently given sequentially
- In adjuvant - asymptomatic decreased EF ab 10% ; symptomatic CHF 2-4%
- Retrospective review community based treatment outside of trials: 4-7 fold increased risk of heart failure for Tz vs no Tz after adjusting for other factors
Trastuzumab Cardiomyopathy

• CHF improves in 75% of pts w ACE & Coreg
• Partially reversible upon stopping treatment some cases without additional medical intervention
• Proper cardiac monitoring – EF q 3mths
• Some patients re-challenged successfully w Tz after EF returns to nl range
• Not all pts recover completely, long term effects and optimal treatment strategy and duration remains to be established
Asymptomatic Patients
Rules for Trastuzumab Continuation
Based on Serial LVEFs

<table>
<thead>
<tr>
<th>Relationship of LVEF to LLN</th>
<th>Absolute Decrease of &lt; 10%</th>
<th>Absolute Decrease of 10 - 15%</th>
<th>Absolute Decrease of ≥ 16%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Within Normal Limits</td>
<td>Cont.</td>
<td>Cont.</td>
<td>Hold *</td>
</tr>
<tr>
<td>• 1-5 % below LLN</td>
<td>Cont.</td>
<td>Hold *</td>
<td>Hold *</td>
</tr>
<tr>
<td>• ≥ 6 % below LLN</td>
<td>Cont.*</td>
<td>Hold *</td>
<td>Hold *</td>
</tr>
</tbody>
</table>

* Repeat LVEF assessment after 4 weeks
  - If criteria for continuation met – resume trastuzumab
  - If 2 consecutive holds, or total of 3 holds occur – discontinue trastuzumab
Sub-clinical Dysfunction
Need to identify early signs of cardiac damage before EF drops

Biomarkers:
- troponin I being predictive of ventricles that -> fail, NPV better than PPV, *Cardinale et al 2000*

- Imaging:
  - Tissue doppler imaging- particularly longitudinal strain predictive of dev LV dysfn - *Sawaya Circ Imaging 2012*
  - TDI and CMR detect pre-clinical changes in EF CMR- hyper enhancement / scar in pts w CMP, - *Fallah-Rad JACC 2011*

- Need more work in this area to validate these abnl as surrogate end points
42 patients → 10 developed CMP (6 month LVEF 64.4% vs. 42.9% [CMP vs. unaffected], p< 0.05)

Lateral wall tissue velocity, global LV strain on echo decreased among patients with CMP

Lateral wall scar (hyperenhancement) present in all 10 patients with CMP (mean 18.4% LV myocardium).

No scar among patients without CMP
Treatment

- Rx with Ace and carvedilol- treat early
- Percentage of adult responders decreases, as time from end of chemo to initiation of treatment increases. No complete recovery of EF was observed when Rx started after 6 months from exposure. Responders showed a lower rate of cumulative cardiac events than non responders- Cardinale JACC 2010
Sunitinib - Sutent

- Targets VEGF receptor
- Cardiac events observed in 11% of pts
- Median time to cardiotoxicity 30.5 weeks = can take weeks to develop
- Pre-eclampsia like syndrome - proteinuria
- HTN in as much as 60% pts (> 150/100)
- Pre-existing CVD seems to pose increase risk for CV events
- Heart failure in 8%, 19% drop EF by 15% or more
- Majority of pts able to resume treatment after holding and implementing standard CHF and aHTN therapy
SUTENT: Targeting Multiple Kinases GIST

Bevacizumab - Avastin

- Monoclonal Abs to VEGF tyrosine kinase
- VEGF likely lowers BP through NO production, necessary for healthy endothelium, disturbs balance between NO and endothelin 1
- High dose leads to hypertension in 1/3 pts
- Proteinuria in 41-63% - via oxidative stress
- Arterial thromboembolic events - suggesting alteration of platelet endothelium interaction
- 2 fold increase in risk of stroke, MI, angina
- LV dysfn 2% on its own, 14% used w AC
- CHF
Cardiovascular MRI

Multiple Applications

- Myocardial scar quant.
- Myocardial viability
- Myocardial iron overload
- Infiltrative cardiomyopathy
- Cardiac neoplasms
- Cardiac thrombus
- LVEF, RVEF

- Vascular Anatomy
- Shunt Fractionation
- Valve Stenosis/Regurgitation
- Myocardial Perfusion
- Coronary Imaging
- Pericardial Effusions
- Pericardial Thickening
Atrial Myxoma

- Most common 1° cardiac neoplasm (~50%)
- Potential hemodynamic, embolic sequelae
- Typical left atrial location, septal attachment via narrow stalk ... LOCATION/MORPHOLOGY CAN VARY!

80% left-sided  10-20% right-sided  <5% ventricular
Rhabdomyoma

- Most common 1° pediatric cardiac neoplasm
- Associated with Tuberous Sclerosis (CNS, dermatologic manifestations)
- Commonly involve the ventricular septum, may be multiple
- Can spontaneously regress
Lymphoma

- Most often aggressive B-cell type
- Increased prevalence in immunocompromised patients
- Large, bulky → anatomic obstruction → dyspnea, edema, tamponade, SVC syndrome
Angiosarcoma

- Most common 1° malignancy
- Slight male predominance, variable age
- Prognosis poor
- Right atrial, pericardial predilection \(\rightarrow\) right heart failure, tamponade
Cardiac Metastases - Modes of Spread

- Direct Invasion: Associated with pulmonary parenchymal involvement (primary, secondary lung Ca)

Non small cell lung cancer infiltrating posterior left atrium
Cardiac Metastases - Modes of Spread

Trans-venous Extension

- Can invade pulmonary veins

Lung adenocarcinoma via left lower pulmonary vein
What does the future hold for Cardio-oncology?

• Further elucidation of mechanisms of cardiac toxicities
• Determine cardiotoxicity of targeted and combination therapy
• Identify predictive markers of cardiac damage, and preclinical signs of cardiac damage – biomarkers, imaging
• Determine major modifiable risk factors that predispose for CT
• Assess risk /benefit in groups w compounding risk factors e.g. the elderly, and for different sub groups
• Define optimal cardioprotective strategies, timing and duration of therapy
• Manage cardiac dysfunction in survivors- large or comprehensive studies for prevention or and prophylaxis
• Genomics- what determines susceptibility and why?
• Design targeted treatments
Reality

CVD

CA
CA/CVD: TWO HEADED MONSTER
MSKCC Cardio-oncology Rotation
EXTRAS
National Cancer Institute- HTN with VSP inhibitors
(e.g. Avastin, Sutent)

• Interdisciplinary CV expert panel
• VSP- include VEGF inhibitors and VEGF receptor blockers
• Conduct formal risk assessment before initiating treatment
• Pre-existing HTN will be common in cancer pts
• Goal for HTN control < 140/90 serious adverse effects documented w unmanaged HTN
• May see increases in BP of 29mHg systolic and 27mmHg diastolic
### Stages of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Patients at high risk for HF but without structural heart disease or symptoms of HF (e.g., patients with hypertension, atherosclerotic disease, diabetes, obesity, and metabolic syndrome or patients using cardiotoxins or with a family history of cardiomyopathy). Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.</td>
</tr>
<tr>
<td>B</td>
<td>Patients who have developed structural heart disease that is strongly associated with the development of HF (e.g., previous myocardial infarction, LV remodeling including LVH and low EF, or asymptomatic valvular disease) but without signs or symptoms of HF.</td>
</tr>
<tr>
<td>C</td>
<td>Patients with structural disease who have current or prior symptoms of HF (e.g., known structural heart disease and shortness of breath and fatigue, reduced exercise tolerance).</td>
</tr>
<tr>
<td>D</td>
<td>Patients with refractory HF requiring specialized interventions (e.g., marked symptoms of HF at rest despite maximal medical therapy—those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions).</td>
</tr>
</tbody>
</table>
Cyclophosphamide

- High doses used for cytoreduction and immunosuppression before bone marrow transplantation can cause acute hemorrhagic pancarditis
- More than 50% have diastolic dysfunction, pericardial effusion, restrictive cardiomyopathy or systolic dysfunction
- Arrhythmias including CHB and VT
- Acute onset CHF 25% of pts receiving high dose
- Acute toxic effects up to 6 dys but generally not long term
### Table 3. Cardiac Events

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total assessable patients</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td>Patients with cardiac event</td>
<td>49</td>
<td>28.3</td>
</tr>
<tr>
<td>Asymptomatic decrease of 20 points, &gt; 50%</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Grade 2 cardiac toxicity (asymptomatic; LVEF range, 40% to 50%)</td>
<td>27</td>
<td>15.6</td>
</tr>
<tr>
<td>Grade 3 cardiac toxicity (symptomatic CHF responsive to intervention; LVEF range, 20% to 40%)</td>
<td>18*</td>
<td>10.4</td>
</tr>
<tr>
<td>Cardiac-related death</td>
<td>1†</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Where we are headed....
<table>
<thead>
<tr>
<th>Trial</th>
<th>Design/Treatment</th>
<th>No. of Patients</th>
<th>Median Follow-Up (months)</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slamon\textsuperscript{74}</td>
<td>Open-label</td>
<td>469</td>
<td>TTP, 7.4 vs 4.6 months; P &lt; .001; OS, 25 vs 20; P = .06</td>
<td></td>
</tr>
<tr>
<td>AC ± trastuzumab</td>
<td></td>
<td>281</td>
<td>TTP 7.8 vs 6.1; P &lt; .001; OS 27 vs 21; P = .16; NYHA III, IV 18% vs 3%</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel ± trastuzumab</td>
<td></td>
<td>188</td>
<td>TTP, 6.9 vs 3.0; P &lt; .001; OS, 22 vs 18; P = .17; NYHA III, IV 2% vs 1%</td>
<td></td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HERA\textsuperscript{76}</td>
<td>Open-label</td>
<td>3,387</td>
<td>12</td>
<td>DFS HR, 0.54; 95% CI, 0.43 to 0.67; P &lt; .0001</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab: 1 year v observation</td>
<td></td>
<td></td>
<td>Distant DFS HR, 0.49; 95% CI, 0.38 to 0.63; P &lt; .0001</td>
</tr>
<tr>
<td></td>
<td>after adjuvant chemotherapy that</td>
<td></td>
<td></td>
<td>OS HR, 0.76; 95% CI, 0.47 to 1.23; P = .26</td>
</tr>
<tr>
<td></td>
<td>included anthracyclines (94%);</td>
<td></td>
<td></td>
<td>Symptomatic CHF 1.7% vs 0.6%; P &lt; .001</td>
</tr>
<tr>
<td></td>
<td>taxanes (28%); and radiation (76%)</td>
<td></td>
<td></td>
<td>NYHA III, IV CHF 0.5% vs 0%, P = .002</td>
</tr>
<tr>
<td>Romond\textsuperscript{75}</td>
<td>Open label</td>
<td>3,351</td>
<td>24</td>
<td>DFS HR, 0.48; 95% CI, 0.39 to 0.59; P &lt; .0001; distant DFS HR, 0.47;</td>
</tr>
<tr>
<td></td>
<td>AC followed by paclitaxel ±</td>
<td></td>
<td></td>
<td>95% CI, 0.37 to 0.61; P &lt; .001; OS HR, 0.67; 95% CI, 0.48 to 0.93;</td>
</tr>
<tr>
<td></td>
<td>trastuzumab (1 year)</td>
<td></td>
<td></td>
<td>P = .015; NYHA III, IV, CHF, 4.1% vs 0.8%; NSABP B-31, 2.9% vs</td>
</tr>
<tr>
<td>Slamon\textsuperscript{77}</td>
<td>Open label</td>
<td>3,222</td>
<td>23</td>
<td>NY831, 0%</td>
</tr>
<tr>
<td></td>
<td>AC followed docetaxel ± trastuzumab (AC-DH) (1 year)</td>
<td></td>
<td></td>
<td>DFS AC plus docetaxel v AC-DH: HR, 0.49; P = .000000005; SCE, 1.2% v 2.3%; P = .05</td>
</tr>
<tr>
<td></td>
<td>Docetaxel/carboplatin trastuzumab (DCH) (1 year)</td>
<td></td>
<td></td>
<td>DFS AC plus docetaxel v DCH: HR, 0.61; P = .0002; SCE, 1.2% v 1.2%; P = 1.00</td>
</tr>
<tr>
<td>Joensuu\textsuperscript{79}</td>
<td>Open-label</td>
<td>232</td>
<td>36</td>
<td>DFS docetaxel or vinorelbine + trastuzumab HR, 0.42; 95% CI, 0.21 to 0.83;</td>
</tr>
<tr>
<td></td>
<td>Docetaxel or vinorelbine ±</td>
<td></td>
<td></td>
<td>P = .01; OS HR, 0.41; 95% CI, 0.16 to 1.08; P = .07; SCE, 0% v 3%</td>
</tr>
<tr>
<td></td>
<td>trastuzumab (9 weeks) followed by FEC</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: AC, doxorubicin and cyclophosphamide; TTP, time to progression; OS, overall survival; NYHA III, IV, New York Heart Association; HERA, Herceptin Adjuvant Trial; DFS, disease-free survival; HR, hazard ratio; CHF, congestive heart failure; NSABP, National Surgical Breast and Bowel Project; SCE, symptomatic cardiac events; FEC, fluorouracil, epirubicin, and cyclophosphamide.
Taxanes

- Abnormalities of cardiac rhythm, conduction and function
- Significant sinus bradycardia, AV block, complete heart block, asystole
- Associated syncope and pre-syncope requiring temp pacing
- Episodes of sustained and non sustained VT, myocardial ischemia
- Hypotension, CHF
Prevention of.... high dose chemotherapy in high risk pt by ACE inhib

• Troponin I soon after HDC marker of poor cardiologic outcomes
• 473 pts- 114 had troponin release soon after HDC- 91, 2, 24, 36, 72 HR)
• High risk factors contra-indication to enrollment
• PE, ECG and echo- abs decrease of more than 10% w decline to under normal ie <50%
Prevention of High Dose Chemotherapy-Induced Cardiotoxicity in High Risk Patients by ACE inhibition

• 114 pts w elevated troponin p chemo randomized
• 1 yr Rx w enalapril or no
• After 1 yr those on enalapril had no significant reduction in EF while untreated did (EF 62% vs 48%)

Cardinale et al, Circulation 2006; 114; 2474-81
• Approx 44% persistently high trop at 1 month
• Enalapril 2.5mg daily increased to 20mg as BP tolerated
• Control group higher incidence of EF reduction and CHF
• Most events w/in 12mths
• ACE potent free radical scavenger
• Anthracycline ? Tissue RAS activation and oxidative stress
Sunitinib

- Pts with cardiac events within 12 months were excluded from trials.
- Pre-existing CVD seems to pose increase risk for CV events
- Baseline and periodic LVEF measurements should be considered.
- If CHF, discontinue.
- If EF is <50% or >20% below baseline, discontinue.
Diagnostic Considerations

- Pseudo-masses
- Thrombus
- Benign Neoplasms
- Malignant Neoplasms
Newest Vascular Disrupting Agents

• Target dysmorphic endothelial cells
  – Disrupt tumor blood supply
  – Tumor endothelium
    • tubulin cytoskeletal network

• Safety profiles
  – Acute coronary syndromes
  – Thrombophlebitis
  – Alterations in hemodynamics
    • Blood pressure, heart rate, conduction
New Vascular-Disrupting Agents

- Designed to disrupt the established vasculature
- Acute coronary and other thrombophlebitic syndromes, BP changes, heart rate, decrease in EF, CPK leaks
<table>
<thead>
<tr>
<th>Structure</th>
<th>Abnormality</th>
<th>Natural History</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardium</td>
<td>Pericarditis</td>
<td>Chronic asymptomatic effusion and/or pericarditis</td>
<td>Fibrous thickening and fluid production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with symptoms: hemodynamic compromise with either constriction or tamponade</td>
<td></td>
</tr>
<tr>
<td>Myocardium</td>
<td>Myocarditis</td>
<td>Progressive diastolic dysfunction and restrictive hemodynamics with symptoms: CHF</td>
<td>Diffuse interstitial fibrosis/microcirculatory damage leading to capillary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>obstruction/extensive fibrosis</td>
</tr>
<tr>
<td>Endocardium</td>
<td>Valvular damage</td>
<td>Over time, progressive stenosis and regurgitation</td>
<td>Cusp and/or leaflet fibrosis</td>
</tr>
<tr>
<td>Vascular System</td>
<td>Arteritis</td>
<td>Premature CAD/accelerated atherosclerosis</td>
<td>Ostial and proximal stenosis; LAD, RCA, and left main more than left circumflex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary hypertension</td>
<td>Pathology similar to atherosclerosis</td>
</tr>
<tr>
<td>Conduction System</td>
<td></td>
<td>All forms of heart block and conduction delay</td>
<td>Fibrosis of the conduction system</td>
</tr>
<tr>
<td>Autonomic Dysfunction</td>
<td></td>
<td>Supraventricular tachycardia; heart rate variability</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; CAD, coronary artery disease; LAD, left anterior descending (coronary artery); RCA, right coronary artery.
<table>
<thead>
<tr>
<th>Sec #</th>
<th>Therapeutic Agent(s)</th>
<th>Potential Late Effects</th>
<th>Risk Factors</th>
<th>Highest Risk Factors</th>
<th>Periodic Evaluation</th>
<th>Health Counseling Further Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>ANTHRACYCLINE ANTIBIOTICS Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone*</td>
<td>Cardiac toxicity Cardiomyopathy Arrhythmias Subclinical left ventricular dysfunction (systolic dysfunction as assessed by ECHO or MUGA)</td>
<td>Treatment Factors Combined with radiation involving the heart Combined with other cardiotoxic chemotherapy: - Cyclophosphamide conditioning for HCT - Amsacrine</td>
<td>Host Factors Black of African descent Younger than age 5 years at time of treatment Treatment Factors Higher cumulative anthracycline doses: - ≥ 550 mg/m² in patients 18 years or older at time of treatment - ≥ 300 mg/m² in patients younger than 18 years at time of treatment - Any dose in infant Chest radiation ≥ 30 Gy Longer time elapsed since treatment</td>
<td><strong>HISTORY</strong> SOB DOE Orthopnea Chest pain Palpitations If under 25 years: Abdominal symptoms (nausea, vomiting) Yearly Info Link: Exertional intolerance is uncommon in patients younger than 25 years old. Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in younger patients.</td>
<td><strong>HealthLinks</strong> Heart Health Counseling <strong>Conducting</strong> Counsel patients with prolonged QTc interval about use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). Counsel regarding maintaining appropriate weight, blood pressure, and heart-healthy diet. Counseling appropriate exercise. Aerobic exercise is generally safe and should be encouraged for most patients. Intensive isometric activities (e.g., heavy weight lifting, wrestling) should generally be avoided. High repetition weight lifting involving lighter weights is more likely to be safe. The number of repetitions should be limited to that which the survivor can perform with ease. Patients who choose to engage in strenuous or varsity team sports should discuss appropriate guidelines and a plan for ongoing monitoring with a cardiologist. <strong>ConsiderationsforFurtherTestingandIntervention</strong> Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Consider excess risk of isometric exercise program in any high risk patient (defined as needing screening every 1 or 2 years).</td>
</tr>
</tbody>
</table>

**SYSTEM = Cardiovascular**

**SCORE = 1**

*Info Link (Mitoxantrone): Although Mitoxantrone technically belongs to the anthrancenedione class of anti-tumor antibiotics, it is related to the anthracycin family and is included here because of its cardiotoxic potential.

Info Link (Dose Conversion): Pediatric studies of anthracycline cardiotoxicity typically describe risks based on combined cumulative doses of doxorubicin. There is a paucity of literature to support isotoxic dose conversion; however, the following conversion factors may be used for convenience in order to gauge screening frequency. Clinical judgment should ultimately be used to determine indicated screening for individual patients. Use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose.

Doxorubicin:
- Multiply total dose x 1
Daunorubicin:
- Multiply total dose x 0.833
Epirubicin:
- Multiply total dose x 0.67
Idarubicin:
- Multiply total dose x 5
Mitoxantrone:
- Multiply total dose x 4
<table>
<thead>
<tr>
<th>Age at Treatment*</th>
<th>Radiation with Potential Impact to the Heart§</th>
<th>Anthracycline Dose†</th>
<th>Recommended Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year old</td>
<td>Yes</td>
<td>Any</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt;200 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥200 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>1-4 years old</td>
<td>Yes</td>
<td>Any</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt;100 mg/m²</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥100 to &lt;300 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>≥5 years old</td>
<td>Yes</td>
<td>&lt;300 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt;200 mg/m²</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥200 to &lt;300 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td>Any age with decrease in serial function</td>
<td></td>
<td>Every year</td>
</tr>
</tbody>
</table>

*Age at time of first cardiotoxic therapy (anhtracycline or radiation [see fields below], whichever was given first)
§See Section 71
†Based on doxorubicin isotoxic equivalent dose [see conversion factors in Section 28 "Info Link (Dose Conversion)"]
### RADIATION

<table>
<thead>
<tr>
<th>Sec #</th>
<th>Therapeutic Agent(s)</th>
<th>Potential Late Effects</th>
<th>Risk Factors</th>
<th>Highest Risk Factors</th>
<th>Periodic Evaluation</th>
<th>Health Counseling Further Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>≥ 40 Gy to: Cranial Nasopharyngeal Oropharyngeal Waldeyer's Ring Spine (cervical, whole) Cervical (neck) Supraclavicular Chest (thorax) Whole lung Mediastinal Mini-Mantle Mantle Extended Mantle TLI STLI TBI*</td>
<td>Carotid artery disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This section is only applicable to patients who:
1) Received radiation to any of the specified fields at ≥ 40 Gy OR
2) Received a combination of radiation to any of the specified fields plus relevant spinal radiation and/or TBI, the sum of which is ≥ 40 Gy

- See dose calculation rules on page 48 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See “Patient-Specific Guideline Identification Tool” in Appendix I to determine specific screening guidelines by section number for individual patients.

### SECTION 66 REFERENCES


Cancer Survivors

• AC toxic effects in long term survivors-> 2 yrs- may or may not have symptoms, may have diastolic, systolic dysfn or both

• Cisplat-direct and indirect effects on CV system, high incidence of hyperlipidemia, obesity and HTN, RR of CVD is increased

• *Info from survivorship here*
Imatinib Mesylate (Gleevec)  
CML, ALL, GIST

- Potently inhibits the kinase activity of Bcr-Abl
- >70% pts with chronic phase CML achieve complete cytogenic remission
- 90% Phila + treated alive at 5 yrs- previously uniformly fatal
- Well tolerated in most
- Clinical trials of the agent
  - peripheral edema -60%, dyspnea in 15% developed LV dysfn and CHF
“Imatinib is cardiotoxic in humans”

Dense membrane whorls
Abnormal mitochondria
Dilated ER
Effaced myofilaments
Most striking is loss of myocardial mass
RECENT DATA
Non-Ischemic Cardiomyopathy

MRI Scar Assessment for Prediction of Chemotherapy Associated Cardiotoxicity???

- MRI, echocardiography, biomarker assessment acquired in patients with breast cancer being rx with trastuzimab/anthracycline-based regimens
- Follow-up for development of cardiomyopathy (“decline of LVEF at least 10% below 55% with accompanying signs/symptoms of CHF”)
MRI Scar Assessment for Prediction of Chemotherapy Associated Cardiotoxicity???

RECENT DATA
Non-Ischemic Cardiomyopathy

MRI in rodents (n=40; rx gp [n=33] 1.5 / 2.5 mg/kg) undergoing weekly doxorubicin infusion. Euthanasia at variable times during 10 week treatment duration.

Low myocardial enhancement predicted absence of ↓ LVEF or death. Increased enhancement associated with LVEF ↓↑ histopathology evidenced intracellular vacuolization, consistent with doxorubicin cardiotoxicity

Novel Approach to Early Detection of Doxorubicin Cardiotoxicity by Gadolinium-Enhanced Cardiovascular Magnetic Resonance Imaging in an Experimental Model
Circ Cardiovasc Imaging 2010;3:550-558; originally published online July 9, 2010:
Benign Neoplasms

- Myxoma
- Papillary fibroelastoma
- Lipomas
- Lipomatous hypertrophy of interatrial septum
- Rhabdomyoma
- Fibroma
- Hemangioma/Lymphangioma
- Paraganglioma
• Initiate for 20mmHg increase in diastolic over baseline
• One large study demonstrated burden of co-morbidities affects the cancer pt as much as stage at time of diagnosis
• monitor BP weekly during first cycle, then Q 2-3wks w subsequent cycles
• BP elevation reversible-> discontinuation or dose reduction may be used to help control VSP induced HTN
• Hold VSP for HTN > 160/100
• For pts discontinuing VSP therapy HTN will dissipate so anticipate need to decrease dose of aHTN
Potential mechanisms and cardioprotective strategies

- Oxidative stress
- Stiffness
- Mitochondrial dysfunction
- Impaired cell survival
- Carvedilol/statins
- ACE inhibitors
- AMPK activators
- Paracrine factors/CPCs
Translation: application of mechanisms to inform imaging markers

- Biologic perturbation
- Anti-angiogenesis
- Sarcomere disruption
- Mitochondrial dysfunction
- Impaired cardiomyocyte survival / fn

- Structural/ Functional Consequences
- Myocardial perfusion
- Diastolic dysfunction/stiffness
- Myocardial energetics / metabolism
- strain
RT and Atherosclerosis

- Accelerated atherosclerosis- RT is trigger for inflammatory reaction- endothelial dysfunction
- 7yrs mean time for -> CAD, 10yrs -> carotid dz
- Atypical locations: CAD - ostial dz, carotids - area of RT
- Approx 75% incidence of carotid dz 17yrs pRT; stroke rate of 12% at 5yrs
- Risk increases w/ increase time from Rx, >30Gy, age < 20yrs at Rx
Differentiating Cardiac Masses

Key Questions

• Where is it?

• Does it impact cardiac function?

• What are its tissue characteristics?
Adjusted Kaplan–Meier Estimates of Survival According to the Underlying Cause of Cardiomyopathy.
Demographics of Cancer Survivors

• Magnitude of population at risk for CVD sequelae is growing, given growing number of cancer survivors

• Estimates are that 60% of adults newly diagnosed with cancer in US are expected to be alive 5 or more years later

• Add 300,000 long term survivors of childhood cancers