Cardiac Toxicities Associated with Cancer Treatment

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Christine Miaskowski, RN, PhD, FAAN
American Cancer Society Clinical Research Professor
and
Sharon Lamb Endowed Chair in Symptom Management Research
Department of Physiological Nursing
University of California, San Francisco
Overview of Presentation

• Epidemiology of cardiac toxicities
• Radiation-induced cardiac toxicities
• Androgen deprivation and cardiac toxicities
• Chemotherapy-induced cardiac toxicities
• Targeted therapy related cardiac toxicities
• ASCO Guidelines for the Prevention and Monitoring of Cardiac Dysfunction in Cancer Survivors
Epidemiology of Cardiac Toxicities

• Cancer and cardiovascular disease are the two leading causes of cancer deaths
  • Responsible for 50% of overall mortality
• Advances in cancer treatments have dramatically improved survival rates
• Newer treatments are associated with deleterious effects on the cardiovascular system
  • Development of cardiovascular events
  • Exacerbation of underlying cardiovascular disease
Epidemiology of Cardiac Toxicities

- Median age of cancer patients has increased
  - Associated with an increase in comorbidities
  - Patient population with an increased number of risk factors
- Risk of CV disease in cancer survivors is greater than that of recurrent malignancy
  - Childhood cancer survivors have a 15-fold increased risk of developing heart failure
  - Childhood cancer survivors have a 7-fold increased risk of premature death due to cardiac events
  - In women with breast cancer, cardiovascular disease is the leading cause of death
Current Challenges

- True estimates of CV toxicities are difficult to determine
  - Patients with CV disease were excluded from clinical trials of newer therapies
- Rapid development and approval of new therapies does not allow for sufficient time for long term follow-up
- “Real life” data has revealed higher incidence rates for CV disease in oncology patients
- Development of cardio-oncologists
- Lack of evidence for monitoring patients and survivors
- Lack of evidence to guide treatment of patients and survivors with CV toxicities
Scope of CV Toxicities

• Virtually all cancer treatments
  • Chemotherapy
  • Radiation therapy
  • Targeted therapies
• Appear to induce CV toxicity through a variety of mechanisms
  • Myocytes
  • Endothelial cells
  • Cardiac conduction system
Types of CV Toxicities

- Direct myocardial injury with or without heart failure
- Systemic hypertension
- QTc prolongation
- Arrhythmias
- Myocardial ischemia
- Hypertension
- Arterial/venous thromboembolic events
- Accelerated atherosclerosis
- Pericardial diseases
- Valvular heart diseases
- CTX drugs can have metabolic effects that increase the risk of CV disease
RT-Induced CV Toxicities

- RT induces vascular endothelial damage
  - Promotes inflammation
  - Accelerates atherosclerosis
- Mediastinal radiation
  - Hodgkin’s lymphoma
  - Breast cancer
  - Esophageal and lung cancer
- Delayed onset of CV disease
  - 10 to 30 years after exposure
- RT affects
  - Coronary arteries, valves
  - Pericardium, conduction system, myocardium
RT-Induced Coronary Artery Disease

• Endothelial inflammation damages the intima and promotes the development of plaques in the coronary arteries
• CAD can develop 5 to 20 years after RT
• Clinical presentation
  • Sudden cardiac death
  • Syncope
  • Acute coronary syndrome
• Indications for CABG are same as for patients without RT
• Need to prevent or reduce traditional cardiac risk factors
  • Diabetes
  • Hyperlipidemia
  • Hypertension
RT-Induced Valvular Disease

- Incidence of valvular disease is difficult to determine
- 81% in patients who received mediastinal radiation
- Valvular disease may be worse in patients who received >30 Gy
- Aortic regurgitation is the most common problem
  - Can occur 20 years after RT
- Valve replacement improves survival
RT-Induced Pericardial Disease

- Common problems
  - Acute pericarditis
  - Pericardial effusion
  - Constriction pericarditis
- Chronic problems occur 3 to 5 years after RT
- Acute pericarditis
  - Rare complication
  - Usually seen with doses of >40 Gy to mediastinum
- Symptoms – chest pain, fever, ECG changes
- Treatment – NSAIDs, steroids
RT-Induced Pericardial Disease

- **Pericardial Effusion**
  - May present months to years after RT
  - Fibrotic changes can occur in the pericardium
  - Effusions can be rapid or slow
  - Result in cardiac tamponade

- **Constrictive pericarditis**
  - Most severe form of pericarditis
  - Occurs 10 years after RT
  - Presents as CHF
  - Initial treatment – diuretics
  - Definitive treatment - pericardectomy
RT-Induced Cardiomyopathy

- Types of cardiomyopathy
  - Restrictive (via myocardial dysfunction)
  - Constrictive (due to pericarditis)
- Occurs 20 years after RT
- Defined as LVEF of less than 50%
- Medical management of HF
  - Beta blockers
  - Angiotensin-converting enzyme inhibitors
RT-Induced Conduction Diseases

- Exact incidence is not known
- Causes of conduction system abnormalities
  - Myocardial fibrosis
  - Ischemia
- Most common condition is right bundle branch block
- AV block is the most serious complication
Androgen Deprivation Therapy

- Cornerstone of treatment for advanced prostate cancer
- Mechanisms for CV disease
  - Obesity
  - Hyperlipedemia
  - Insulin resistance
  - Metabolic syndrome
  - Acute kidney injury
  - Hypecoagulability
  - Atherosclerosis
Androgen Deprivation Therapy

- At physiological levels, testosterone is cardioprotective
  - Decreased in atherosclerosis
  - Increased arterial compliance
- Findings from studies on the relationship between androgen deprivation therapy and increased CV risk are inconsistent
  - High risk elderly were excluded from most trials
Anthracycline-Induced CV Toxicities

- Anthracycline regimens (doxorubicin)
  - Causes breaks in DNA – cardiac cell death
- Associated with LV dysfunction
  - Cardiomyopathy
- Acute toxicity
  - Primarily arrhythmias – atrial fibrillation
- Chronic toxicity
  - CHF
  - Not reversible
- Two thirds of asymptomatic childhood cancer survivors had evidence of cardiomyopathy
  - Warrants ongoing monitoring
Risk Factors for Anthracycline-Induced Cardiomyopathy

- Cumulative dose $>500$ mg/m$^2$
- Age $>60$ years
- Hypertension
- Previous heart disease
- Previous radiation therapy
- Concurrent CTX
- Hematopoietic cell transplant
- Obesity (BMI $>30$)
- Diabetes
Alkylating Agents – CV Toxicity

• Cyclophosphamide
  • Dose dependent reduction in LV function
  • Acute cardiomyopathy (days to weeks)
  • High dose – 180 mg/kg over 4 days
    • 28% incidence rate
• Ifosfamide
  • Supraventricular arrhythmias can occur
  • Acute and dose dependent reduction in LV function (16 to 18 g/m² – 33% to 67% of patients)
Trastuzumab-Induced CV Toxicities

- Herceptin is a monoclonal antibody that targets HER2
- Standard treatment for patients with HER2 positive breast cancer
- Mechanism for LV dysfunction is not clear
- Exact incidence is not clear
  - 3% when given alone
  - 5% when given after anthracyclines
  - 27% when given concurrently with anthracycline
- Considered to be reversible cardiotoxicity
Risk Factors for Trastuzumab-Induced Cardiomyopathy

- Age >50 years
- Hypertension
- Concurrent CTX
- Obesity (BMI >30)
- Lower baseline ejection fraction (≤55%)
- Diabetes
- Smoking
Protein Kinase Inhibitors - CV Toxicities

• PKIs target tyrosine kinases
• PKIs that target the VEGF receptor can cause cardiomyopathy
• Sunitinib
  • 28% risk of asymptomatic HF
  • 15% risk of symptomatic HF
  • Not entirely clear if the HF is reversible
Protein Kinase Inhibitors - CV Toxicities

• Lapatinib
  • Targets EGFR and HER-2 kinases
  • 1.6% of patients had >20% decline in LV function
  • 0.2% experienced symptomatic HF
  • Appears reversible

• Imatinib
  • HF is rare but associated with increased age and pre-existing CV risk factors
ASCO Guidelines for Prevention and Monitoring
_JCO 35(8):893-911, 2017_

- Focus on cardiac dysfunction
  - Primarily HF
- Evidenced-based guidelines
- Multidisciplinary expert panel
- Weighed the consistency of the evidence
- Recommendations based on an analysis of benefits versus harms
Fig 1. Overarching clinical questions addressed in the clinical practice guideline.
Patients at Increased Risk for Cardiac Dysfunction - 1

- High dose anthracycline treatment
  - Doxorubicin ≥250 mg/m²
  - Epirubicin ≥600 mg/m²
- High dose RT (≥30 Gy) where the heart is in the treatment field
- Lower dose anthracycline in combination with lower RT dose where the heart is in the treatment field
Patients at Increased Risk for Cardiac Dysfunction -2

• Treatment with lower dose anthracycline or trastuzumab alone, and the presence of any of the following risk factors
  • Multiple cardiac risk factors (≥2) including: smoking, hypertension, diabetes, dyslipidemia, during or after completion of treatment
  • Age ≥60 years
  • Compromised cardiac function at any time during treatment
    • Borderline low LVEF – 50% to 55%
    • History of MI
    • Moderate valvular heart disease
Patients at Increased Risk for Cardiac Dysfunction - 3

• Treatment with lower dose anthracycline followed by trastuzumab
• Sequential therapy
• No recommendation was made regarding the administration of kinase inhibitors
Fig 1. Overarching clinical questions addressed in the clinical practice guideline.
Minimize Risk BEFORE Treatment

- Avoid or minimize use of potential cardiotoxic therapy if alternatives exist
- Perform a comprehensive assessment of patients and screen for CV disease risk factors
  - Hypertension
  - Diabetes
  - Dyslipidemia
  - Obesity
  - Smoking
- Obtain an echocardiogram before treatment
Fig 1. Overarching clinical questions addressed in the clinical practice guideline.
Minimize Risk DURING Treatment - 1

- Screen and manage CV disease risk factors
  - Hypertension
  - Diabetes
  - Dyslipidemia
  - Obesity
  - Smoking
- In patients who will may receive high dose anthracyclines (i.e., doxorubicin $>250$ mg/m$^2$, epirubicin $>600$ mg/m$^2$)
  - Use liposomal formulation of doxorubicin
  - Use a continuous infusion of anthracycline
  - Administer dexrazoxane (cardioprotectant)
Dexrazoxane

• Cardioprotectant
• July 2011 – FDA restricted its use
• Increased rate of secondary cancers and acute myelogenous leukemia in pediatric patients
• Mechanism of action
  • Chelates iron
  • Reduces the number of metal ions complexed with anthracycline
  • Decreases the formation of superoxide radicals
Minimize Risk During Treatment - 2

- For patients who require mediastinal RT
  - Lowest dose possible
  - Use more tailored and precise RT fields that exclude the heart as much as possible
  - Use deep inspiration breath holding
Fig 1. Overarching clinical questions addressed in the clinical practice guideline.

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Monitoring DURING Treatment - 1

- Careful history and physical exam
- If patient has clinical signs/symptoms of cardiac dysfunction
  - Echocardiogram
  - Cardiac MRI or MUGA scan if echocardiogram is not available
  - Serum cardiac biomarkers (troponins, natriuretic peptides)
- Referral to a cardiologist
Monitoring DURING Treatment - 2

- For asymptomatic patients considered to be at increased risk
  - Echocardiogram for monitoring
  - Frequency of monitoring is based on clinical judgement
- No recommendation could be made on discontinuation of treatment
  - Collaboration with cardiologist, oncologist, and patient
- Use echocardiogram surveillance in patients with breast cancer receiving trastuzumab
  - Frequency at clinicians discretion
Fig 1. Overarching clinical questions addressed in the clinical practice guideline.
Monitoring AFTER Treatment - 1

- Careful history and physical exam
- If patient has clinical signs/symptoms of cardiac dysfunction
  - Echocardiogram
  - Cardiac MRI or MUGA scan if echocardiogram is not available
  - Serum cardiac biomarkers (troponins, natriuretic peptides)
  - Referral to a cardiologist
Monitoring AFTER Treatment - 1

• In asymptomatic patients who are at increased risk for cardiac dysfunction
  • Perform an echocardiogram between 6 and 12 months after completion of treatment
• Patients identified with asymptomatic cardiac dysfunction
  • Refer to cardiologist or cardio-oncologist
LIFESTYLE MODIFICATIONS

• Management of cardiovascular risk factors
  • Smoking
  • Hypertension
  • Diabetes
  • Dyslipidemia
  • Obesity
• Healthy lifestyles
  • Diet
  • Exercise
  • Stress reduction
• Maintenance of a high index of suspicion