Cardio-Oncology: An Emerging Subspecialty

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Introduction

- As longevity has increased and cardiac mortality has decreased, cancer has become more common.
- Risk factors for heart disease and cancer have significant overlap.
- Many patients now living with both diseases.
- Chemotherapy and radiation therapy have potential deleterious effects on the heart.

Cardiac Effects of Chemotherapy: Anthracyclines

- Anthracyclines are best known and documented cancer agents with cardiac toxicity.
  - Doxorubin, Daunorubicin, Idarubicin, Epirubicin

- Types of Anthracycline cardiac toxicity:
  - Acute/subacute – drug initiation to several weeks later.
    - Less common than chronic
    - Generally more mild
      - Atrial fibrilaltion, HF, myocarditis, ischemia
  - Chronic – 2 types
    - Early – less than 1 year
      - More common
    - Late – more than 1 year
    - Characterized by decline in EF with or without HF symptoms
    - Peak time = 3 months after last dose

Anthracycline Cardiac Toxicity

- Mechanism
  - Not completely clear
  - Free radical/oxidative stress leads to myocyte injury
  - AC binds to Topoisomerase II and DNA, causing cell death
    - Alpha subtype – in tumors
    - Beta subtype – in cardiomyocytes

- Risk factors
  - **Cumulative Dose!**
    - <400 mg/m2 – 0.14%
    - 550 mg/m2 – 7%
    - >700 mg/m2 – 18%
    - Long term f/u studies suggest even higher risk.
  - Age at exposure – bimodal distribution
    - Children – 38% abnormal echos at >10 y f/u.
    - Elderly
  - Paclitaxel
  - Trastuzumab
  - Chest radiation
  - CAD, HTN, PAD, DM
  - Longer duration of survival

Decreasing the Risk of Anthracyclines

- Limiting cumulative dose to maximum of 450-500 mg/m2 in adults
- Bolus infusion higher risk than continuous infusion, but
  - Less toxic for tumor as well
  - Needs central line and hospitalization
- Alterations to molecule
  - Epirubicin
  - Mitoxanthrone
  - Liposomal encapsulation
  - Give with Dexrazoxane (Fe chelator)
- Prophylactic Beta-blockers and ACE-inhibitors
- Monitoring of heart function
  - Cornerstone of prevention
  - Baseline LVEF – unless low dose planned
  - Echo or MUGA
  - Follow-up schedule without clear guidelines
  - Decrease in LVEF by 10% to below 55% or any drop to below 45% significant; alter therapy
  - Tn and BNP gaining interest, not definitive
- Treatment of low EF
  - Standard therapy with BBl and ACEI.

Non-Anthracycline Chemotherapy and the Heart: Trastuzumab

- Trastuzumab (Herceptin)
  - Targets Human Epidermal Growth Factor -2 (HER-2)
  - 15-20% Breast tumors overexpress HER2
  - Causes LV dysfunction
    - Usually asymptomatic
    - Severe HF rare
    - Idiosyncratic
    - Not dose related
    - Often reversible with discontinuation
    - Rechallenge after recovery often tolerated well
    - Cardiac biopsy – no necrosis
- Risk of decreased EF
  - T alone – 3%
  - T + paclitaxel – 7%
  - T + anthracycline – 13%
  - T + cyclophos – 27%
- Check baseline LVEF
  - Monitoring schedule unclear but intermittently through 18 mos or if any symptoms

Non-Anthracycline Chemotherapy and the Heart: 5-Fluorouracil

- 5-Fluorouracil
  - Causes chest pain
  - Incidence about 2%
  - Review of 377 cases
    - Angina 45%
    - MI 22%
    - Arrhythmia 23%
    - Pulm Edema 5%
    - Cardiac arrest 1.4%
    - Pericarditis 2%
- Capecitabine metabolized to 5-FU
- Mechanism
  - Presumed vasospasm
- Treatment
  - Stop infusion
  - Standard angina therapy
- 47% recurrence with rechallenge

Non-Anthracycline Chemotherapy and the Heart: Miscellaneous Agents

- Tyrosine Kinase Inhibitors
  - Sorafenib and Sunitinib
  - Rare but definite risk of LV dysfunction and HF.
- Alkylating agents
  - Cyclophoasphamide, Ifosfamide, Cisplatin, Busulfan
  - Acute cardiomyopathy with high doses (rare)
- Other agents with rare cardiac effects
  - Fludarabine
  - Methotrexate
  - Vinca alkyloids
  - Paclitaxel

Radiation Therapy and the Heart

- Most commonly with Hodgkin's lymphoma or left sided breast cancer.
- Care now taken to avoid direct cardiac irradiation.
  - Patients may present now with problems related to radiation decades earlier.
- Can be a very late effect, >25 years after radiation.
- May affect any and all heart structures
  - Coronary arteries
    - CAD, diffuse and severe
  - Valves
    - Stenosis
    - Regurgitation

  More Common

  - Myocardium
    - Restrictive cardiomyopathy
  - Conduction system
    - Heart block, arrhythmia
  - Pericardium
    - Constrictive pericarditis
    - Pericardial effusion

  Less Common

Cardio-Oncology: Conclusions

- Increasing number of patients with concomitant heart disease and cancer.
- Anthracycline toxicity most well known complication of chemotherapy
  - Dose related
  - Onset peak 3 months after last dose but can present very late
  - Causes a cardiomyopathy
  - Treat with standard HF drugs
  - Monitoring of LVEF during therapy important means of reducing risk
  - Be aware of young adults treated as children with AC. Intermittent LVEF monitoring warranted.
- Herceptin causes transient decrease in LVEF.
  - Monitoring on therapy reasonable.
- Radiation therapy may affect any heart structure
  - CAD and valves most common
  - May occur quite late.
- Movement at large cancer centers around the country to establish Cardio-Oncology clinics to optimize prevention and treatment strategies for these patients.