Chemotherapy and Cardiomyopathy

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I Have No Disclosures

Objectives

- Understand definition chemotherapy induced cardiomyopathy (CIMP)
- Role of imaging in the management of CIMP
- Therapies and treatment strategies to minimize risk of CICM

Introduction

- Heart disease and cancer are the top 2 leading causes of death in the United States.
- Modern cancer therapy has successfully cured many cancers and converted a terminal illness into a chronic disease.
- Cancer and CAD patients often overlap
- Cardiologist and oncologist should work together to identify risk factors.

Cardiovascular complication include:

- Heart failure
- Myocardial Ischemia
- HTN
- Pulmonary HTN
- Pericardial disease
- Thromboembolism
- QT prolongation and arrhythmia
- Radiation induced cardiovascular disease

Heart Failure

- Daunorubicin effects known for a long time (first anthracycline class of chemotherapy)
- New agents such as Trastuzumab and proteasome inhibitors also cause cardiomyopathy
- 1-5% of cancer survivors develop chemotherapy induced cardiomyopathy and have the worst survival rates among cardiomyopathies.
- Early diagnosis and treatment reduces risk.

Definition of chemo related cardiotoxicity:

- Decrease in ejection fraction globally or with regional wall motion abnormalities
- Heart failure symptoms
- Heart failure signs (s3, tachycardia, or both)
- Decline in initial EF of at least 5% to less than 55% with sign and symptoms
- Decline in initial EF of at least 10% to less than 55% in asymptomatic patients

Incidence and pathogenesis:
Anthracyclines

- Doxorubicin related HF was found to be 5% at cumulative dose of 400mg/m2, 16% at 500mg/m2 and 26% at 550mg/m2
- Up to 30% reported HF symptoms 13 years after treatment (dose range 180-240mg/m2)
- There is no safe dose of doxorubicin (even loses as low at 100mg/m2 reported HF symptoms)
- Doxorubicin poisons topoisomerase 2 to cause DNA strand to break in both cancer cells and in cardiomyocytes.
- There is increased reactive oxygen species and decrease in midochondria

Incidence and pathogenesis
Alkylating agents (cyclophophamide)

- Add alkyl group to DNA of rapidly dividing cells and inhibit DNA replication and cell proliferation
- Cause arrhythmia and EKG changes that occur within 1-2 weeks and can resolve spontaneously
- HF reported as up to 28% who had cyclophosphamide therapy

Incidence and pathogenesis
HER-2 pathway

- Trageted therapies against HER-2 pathway:
  - Trastuzuman is a monoclonal antibody against human epidermal growth factor receptor tyrosine kinase (HER2 or ErbB2) which regulate cell growth and repair.
  - Over expression of HER2 occurs in 25% breast cancer and confers increased proliferative and metastatic potential
  - Trastuzumab administrated to HER2 positive breast cancer patient had a 33% reduction in mortality and increased median survival by 5 months

Incidence and pathogenesis
HER-2 pathway (trastuzumab)

- Trageted therapies against HER-2 pathway:
  - 1-4% trastuzumab treated patient developed heart failure
  - When cyclophosphamide was added, the incidence of heart failure increased to 27%
  - Symptoms improved 4-6 weeks after stopping trastuzumab

Incidence and pathogenesis
VSP pathway (bevacizumab)

- Vascular endothelial growth factor (VEGF) signaling pathway inhibit downstream kinase which results in:
  - HTN
  - cardiomyopathy
  - conduction abnormalities
  - acute coronary syndromes
  - arterial thromboses
- Heart failure due to VSP inhibitors is reversible with cessation of therapy

Incidence and pathogenesis
Protesome inhibitors (bortezomib)

- Proteasome inhibitors blocks cell proliferation and induces apoptosis in tumors (especially multiple myeloma)
  - known to cause or worsen heart failure and ischemia
  - reversible with cessation of therapy and HF treatment

Screening, Risk Stratification and Early detection:

- Identify patients early and treat according to guidelines
- EF assessment is mandatory to establish baseline before cancer treatment started
- Echocardiogram is preferred modality
- MUGA has less interobserver variability but radiation exposure limits use
- EF assessment should be made using the biplane method of discs according to American Society of Echocardiography guidelines
- Use contrast echocardiography if necessary

Screening, Risk Stratification and Early detection:

- CICP defined as drop of EF by
  - >10%
  - or >5% with HF symptoms

- Accurate measurement is necessary

Early detection:
Role of echocardiography

- Myocardial strain helps estimate global and regional myocardial mechanical function and can detect early signs of LV dysfunction:
  - Tissue doppler imaging —> user and angle dependent
  - Speckle tracking strain imaging—> angle independent
  - Strain can pick up changes 3 months before LV dysfunction. Changes can be noted several years after exposure.

Early detection:
Role of biomarkers

- Troponin show good correlation of elevated enzymes with LV dysfunction in anthracycline treated patients
- BNP have showed to have mixed results but several studies have indicated that these peptides could be good early indicators of cardiac damage.
- BNP is usually transient during anthracycline treatment and those with persistently elevated levels developed heart failure.

Prevention:
anthracyclin induced CM

- Select nonanthracycline regimen (docetaxel, carboplatin, and trastuzumab) 5-year survival was 81%

- Anthracycline regimen (doxorubicin, cyclophosphamide, docetaxel, trastuzumab) 5 year survival was 84%
  - replace bolus administration with slow infusion (6hours or longer)

  - use PEGylated liposomal doxorubicin has selective uptake by tumors cells and less free floating which decrease side effects. However this delivery system is expensive

Prevention:
anthracyclin induced CM

- Dexrazoxane is protective against anthracycline induced toxicity.
- However one trial has shown lowered efficacy of athracycline.
- FDA approved dexrazoxane use for patients who received more than 300 mg/m2 for metastatic breast cancer.
- Increased risk of second malignancies in pediatric cancer survivors

Prevention:
trastuzumab induced CM

- Avoid concurrent use with anthracyclin
  - up to 27% incidence of heart failure reported

Treatment

- Identify high risk patients early and monitor symptoms closely.
- There is no threshold anthracycline dose below which cardiotoxicity does not occur.
- Slow infusion (>6hr) compared to short bolus of anthracycline has lower incidence of heart failure

Treatment

- ACE inhibitors and beta blocker use decrease incidence of heart failure and allow for completion of chemotherapy
- Carvedilol and nebivolol have anti-oxidative properties which have shown to attenuate changes
- Prophylactic neurohormonal blockade has shown smaller decrement in LV ejection fraction
- In small studies, statin therapy seems to be helpful. Lower rate of HF hospitalization and lower decline in LV function.

Treatment

- Ranolazine which limits intracellular calcium influx has been shown to decrease anthracycline toxicity
- Other agents with antioxidant effects have shown benefit in reducing anthracycline toxicity in animal models
  - Metformin, bioflavonoids, L-carnitine, alpha-linoleic acid

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Conclusion

- In the current chemotherapy era, many cancers have been converted from terminal to chronic disease. Cardiologists and oncologists should work together to identify patient risk factors early.
- Cancer treatment should not be withheld due to cardiac risk factors
- Effects of chemotherapy can manifest years after treatment has finished
- Echocardiogram plays a pivotal role in management. Establish protocol utilizing newer techniques such as speckled tracking and strain.

Resources

- cardioonc.org
- ACC cardio-oncology section

References

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