BASELINE RISK FACTORS FOR CARDIOTOXICITY

SCREENING, RISK STRATIFICATION AND EARLY DETECTION STRATEGY

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Introduction

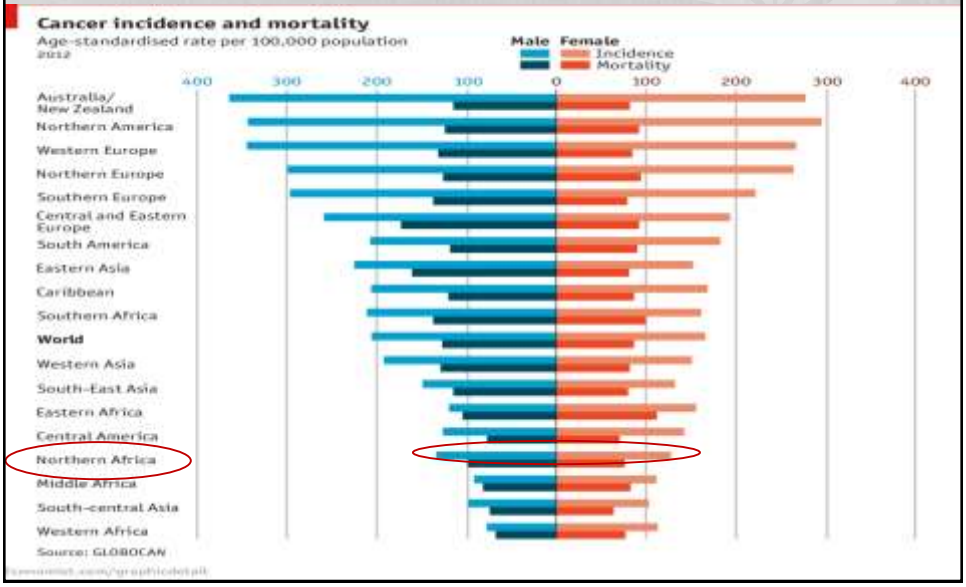
- Cancer therapies may have short-term and long-term side effects involving the heart and circulation, as well as exacerbating and/or unmasking existing heart disease.
- The development of CV disease during the course of cancer treatment can adversely impact the management of the underlying malignancy by interfering with the optimal doses and timing of lifesaving cancer therapy.
- In addition, the development of a potentially important cancer therapy may be halted or abandoned because of a perceived increased CV risk.

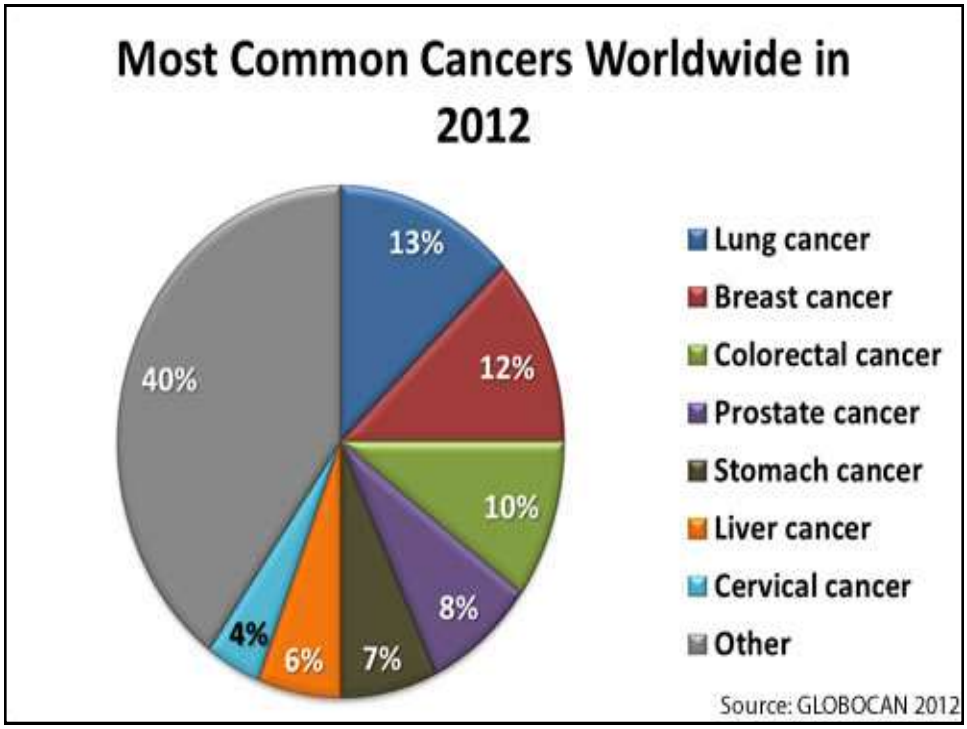
The discipline of cardio-oncology has developed in response

Introduction

- The incidence of cancer treatment-induced CV injury varies widely, depending on the specific cancer therapy used, duration of therapy, and underlying patient comorbidities.
- In a recent comprehensive review of breast cancer survivors in the United States, women were noted to be at significantly increased risk of death caused by CVD, exceeding their risk of death from the initial cancer itself or from recurrent disease.

Magnitude of the problem





Risk factors for cardiotoxic complications

Factors related to the patient

- Younger than 18 or older than 65 at the time of treatment
- Age at Diagnosis
- Time since Therapy
- Pregnancy/delivery
- Risk factors for CV disease (smoking, diabetes, obesity, dyslipidemia)
- Prior cardiovascular disease & risk factors for HF (previous MI, angina, diabetes)

Factors related to therapy

- Rapid drug infusion
- Combination of drugs
- Receiving radiation therapy to the head , neck and thorax
- Receiving increasing or cumulative doses of some chemotherapeutics

Risk factors for cardiotoxic complications

Factors related to the disease

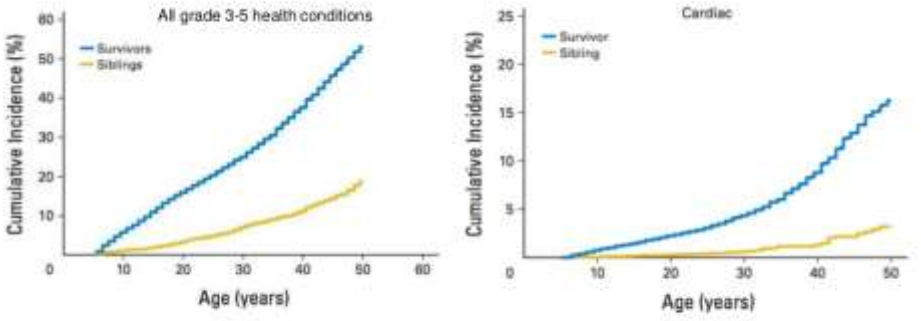
Cancer treatment could bear the risk of cardiac toxicity due to the fact that:

- **Some cancers need aggressive therapy**
  - Leukemias
  - Certain types of lymphomas
  - Lung cancer
- **Some cancers are potentially curable**
  - Breast cancer
  - Hodgkin's disease

  Giving the patient the chance to live so many years after the termination of therapy, allowing the development of long term complications; including cardiac ones (cardiac risk increases up to 25 times)

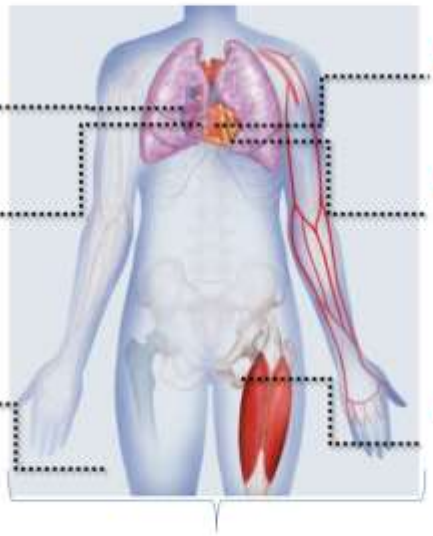
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Aging and Risk of Severe, Disabling, Life-Threatening, and Fatal Events in the Childhood Cancer Survivor Study



Armstrong et al. *J Clin Oncol* 2014

Cancer Therapy Effects on CV System



- Coronary artery disease / MI
- Valvular / pericardial disease
- Peripheral artery disease
- Cardiomyopathy / heart failure
- Conduction dz / arrhythmia / autonomic dysfunction
- Venous thrombosis
- Exacerbation of known CV risk factors

Cancer therapy bearing cardiotoxicity potential

Cardiac myocytes have limited regenerative capacity, so they are susceptible to permanent side effects

- **Chemotherpaeutic drugs**
  - Anthracyclins
  - Alkylating agents
  - Antimicrotubule agents
- **Targeted therapy**
  - ATRA (AML-M3)
  - Nilotinib (CML)
  - Herceptin (Breast cancer)
- **Radiation therapy**
  - Especially to the head, neck and chest areas

Cardiotoxic chemotherapeutics

Anthracyclins, Anthraquinones

- Incidence is dose dependent
- Acute (myopericarditis), subacute and chronic
- Once developed, carries poor prognosis and often fatal
- Manifestations resembling dilated cardiomyopathy

Vinca alkaloids (vinblastine)

- Hypertension, myocardial ischemia, myocardial infarction, and other vaso-occlusive complications

Topoisomerase II inhibitors

- Myocardial infarction and vasospastic angina

Alkylating agents (cyclophosphamide)

- At low doses, not reported to be associated with cardiotoxicity
- Acute cardiac toxicity (fulminant CHF) in high dose conditioning regimens for BMT

Antimetabolites (5-FU)

- The most widely investigated antineoplastic agent known to cause myocardial ischemia
- Ischemic events are more common when administered in combination with cisplatin

Cardiotoxic Targeted Therapy

All Trans Retinoic Acid (ATRA) (AML-M3)

- 10% to 15% of patients develop a retinoic acid syndrome (RAS), manifested by fever, dyspnea, pleural effusions, pericardial effusions (with potential for cardiac tamponade), pulmonary infiltrates, peripheral edema, and myocardial ischemia/infarction

Ritoximab (B-lymphoproliferative disorders)

- Arrythmias
- Few reported infusion-related deaths secondary to cardiogenic shock

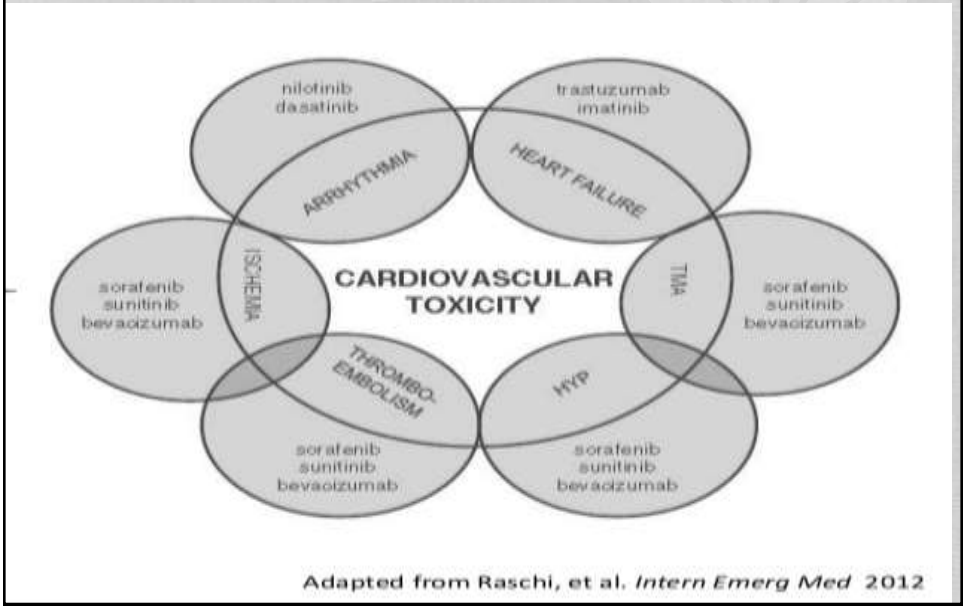
Imatinib, Nilotinib (CML)

- CHF, arrythmia

Herceptin (Breast cancer)

- Increased incidence of CHF when combined with chemotherpeutics
- LV dysfunction, which has a high reversibility potential

Emerging cardiotoxicity of Targeted Therapy



Adapted from Raschi, et al. *Intern Emerg Med* 2012

Radiation Therapy

- High-energy radiation administered internally or externally
- Cancer cells are killed by damaging their DNA or creating free radicals within the cell that lead to DNA damage
- Normal cell DNA is damaged in the process so proper placement of radiation is crucial
- Irradiation of a substantial volume of the heart to a sufficiently high dose can damage virtually any component of the heart, including:
  - pericardium
  - Myocardium
  - heart valves
  - coronary arteries
  - Capillaries
  - and conducting system

- Location: the closer the radiation is to the heart, the more potential damage it will cause, as in:
  - Radiation to left breast cancer
  - Radiation to cervical and axillary lymph nodes in H.D.
- Dose-related response: major cardiac events rate increases with increased dose
- Pericarditis is the typical acute manifestation of radiation injury
- Other manifestations including:
  - Chronic pericardial disease
  - Coronary artery disease
  - Cardiomyopathy
  - Valvular disease
  - Conduction abnormalities

  can manifest years or decades after the original treatment.
- These complications can cause significant morbidity or mortality

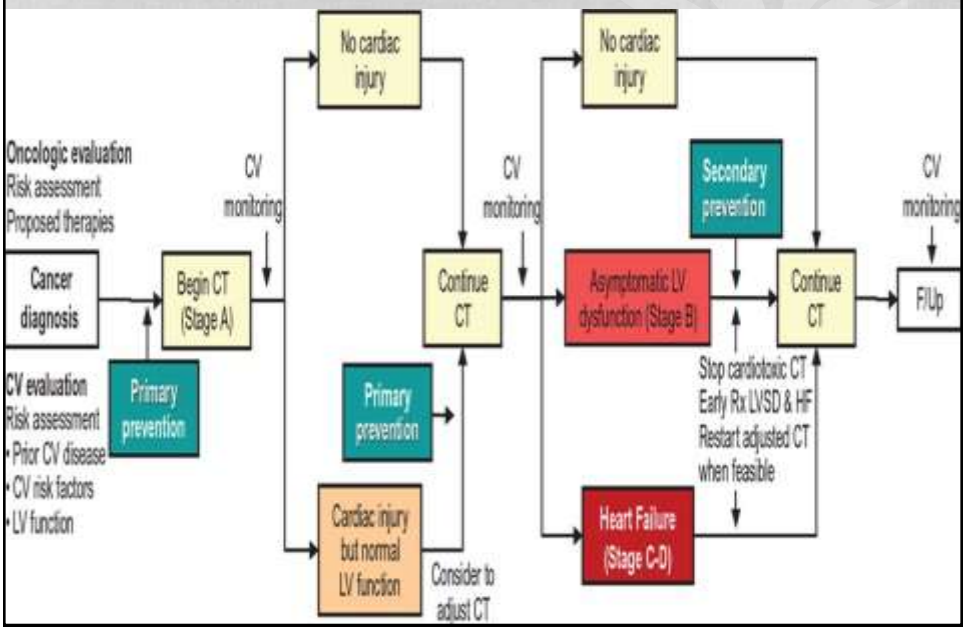
Monitoring Cardiac Toxicity and early detection stratgies

During cancer treatment, close cardiovascular monitoring should be applied for the early detection of cardiac toxicity, re-evaluation of the initial therapeutic plan, and early treatment of any cardiac dysfunction

Subclinical cardiac changes

- Long before the onset of clinically significant cardiac events occurring many years after treatment, some subclinical cardiac changes can occur over weeks, months or first years
- can be detected either based on functional dysfunction or anatomical modification measurements.

Cardiotoxicity prevention plan



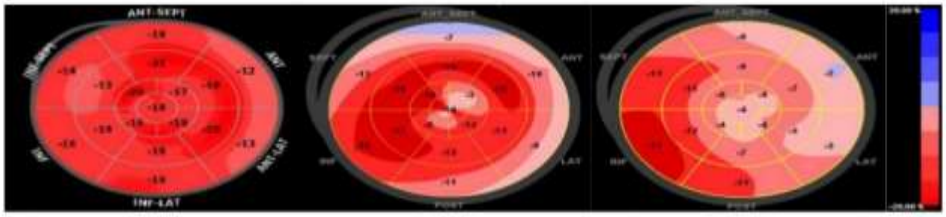
Echocardiography

Global Longitudinal Strain and strain rate (GLS)
Ejection fraction (EF)
Limitation:

- Not ideal for asymptomatic patients
- 47% of CHF is diastolic in nature, occurring with a preserved LVEF

Early detection

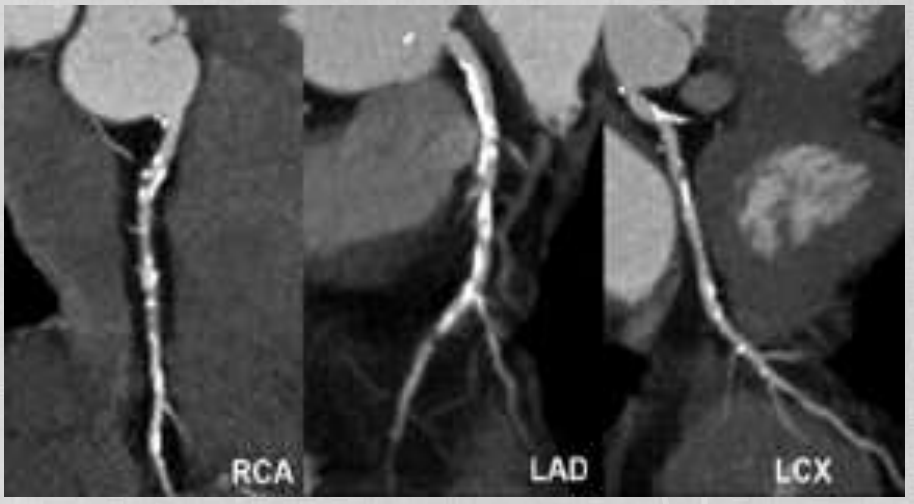
Longitudinal Strain vs. 3D Echo LVEF



Post-TCPH		Trastuzumab x 3M		Trastuzumab x 5M	
Pre-Trastuzumab		Pre-Pertuzumab		Pertuzumab x 2M	
LVEF	54%	LVEF	53%	LVEF	29%
GLS	−17%	GLS	−11%	GLS	−7%

CCTA

calcification of the coronary arteries and determination of calcium score
vulnerable lipid-rich soft plaques



Circulating biomarkers

- Used to determine high risk patients before drug administration to start preventive measures beforehand
  - *N-terminal pro-B–type natriuretic peptide* (NT-proBNP)
  - *troponin* (TnI)
  - *C-reactive protein*

Other modalities

- MRI
- Biopsy
- Scintigrahy &MUGA

Primary Prevention Measures

Modifying Chemotherapy Administration and newer irradiation techniques

Changes in the dose, the pharmacological structure, and the schedule of chemotherapy administration , also usage of newer radiation machines and techniques.

Exercise

Ongoing trials are currently studying the effect of different levels of training and the preventive efficacy of exercise 24 hours before every chemotherapy cycle, aiming to increasing cardiovascular reserve

Primary Prevention Measures

Administration of Cardioprotective Drugs

- Antioxidants Iron chelators ACE inhibitors and β blockers

Cardioprotective Strategies

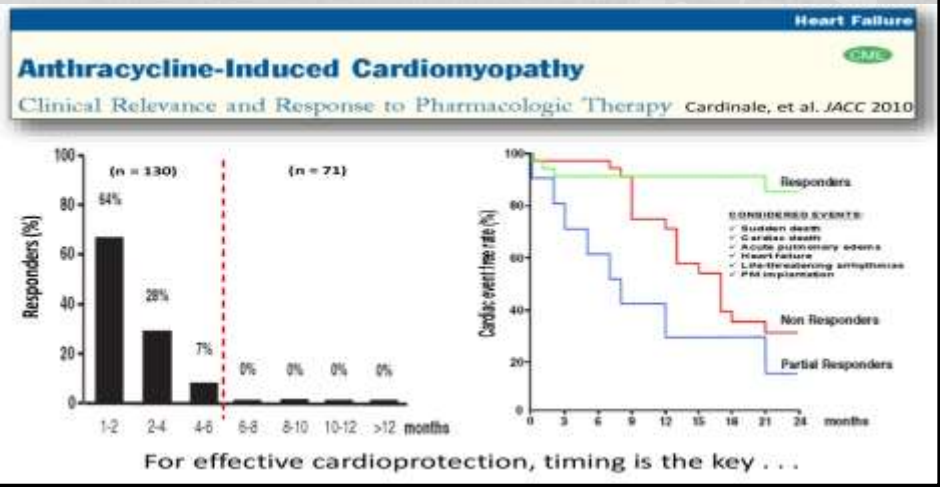
Anticancer Therapy	Mechanism of Protection	Mechanisms of Action	Level of Evidence
Anthracyclines	Dexrazoxane	↓ROS via ↓anthracycline-Fe formation, ↓DNA damage via ↓Top2β-DNA cleavage	Animal studies, RCTs, Meta-analyses
	Statins	↓Cell death, ↓Top2β-DNA damage	Animal/Retrospective studies
	β-Blockers	↑Pro-survival signaling via β-arrestin, ↓Oxidative stress, ↑Lusitropy	Small RCTs
	ACE Inhibitors	↓Oxidative stress/ interstitial fibrosis; ↑Ca handling, ↑cardiomyocyte metabolism, ↑mitochondrial function	Small RCTs
	Exercise	↓ROS formation, ↓apoptosis; ↑Ca handling, myocardial energetics	Animal studies
	Neuregulin	Biased ErbB signaling	Animal studies
Trastuzumab	ACE Inhibitors β-Blockers Exercise	↓Angiotensin blockade of NRG-1/ErbB ↑Pro-survival signaling via β-arrestin, EGFR ↑NRG-1/ErbB, ↑myocardial Akt, ↓TGF-β	Retrospective studies Retrospective studies Small study
Angiogenesis Inhibitors	Thalidomide AMPK activators	↑Pericyte function via PDGFR ↑Favorable myocardial energetics	Animal studies Animal studies

Adapted from Hahn, et al. *JAHA* 2014

Primary Prevention Measures

Genetic Testing

polymorphisms in genes involved in anthracycline absorption, and metabolism have an impact on the risk of anthracycline-induced cadiotoxicity



For effective cardioprotection, timing is the key . . .


THANK YOU