Cardiovascular Toxicity of Anti-cancer treatment

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Effect of Chemotherapy on the heart:

1. Myocardial dysfunction causing heart failure
2. Coronary artery disease
3. Valvular Disease
4. Arrhythmias
5. Arterial hypertension
6. Pulmonary hypertension
7. Thromboembolic manifestations

Myocardial dysfunction

- Myocardial dysfunction and Heart failure are the most concerning cardiovascular complications of cancer therapies.
- The time point when cardiotoxicity becomes clinically manifest varies substantially; some cancer treatments induce side effects that appear early after exposure while others generate cardiac injuries resulting in clinical problems only years later.

Incidence of Myocardial dysfunction after chemo therapy

1. Anthracyclines (Doxorubicin)(Adriamycin)

   Ranges from 3 % in low doses up to 48 % in higher doses.
2. Alkylating agents (Cyclophosphamide)

   7-28%
3. Monoclonal antibodies (Trastuzumab)

   Up to 20 %
4. Tyrosine kinase inhibitors (Sunitinib)

   Up to 19 %

Who Is at risk????

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1. Pediatric population
2. Elderly
3. Diabetes mellitus
4. Hypertension
5. Dyslipidemia
6. Family history of Premature Cardiovascular disease
7. Smoking
8. Obesity
9. Hight alcohol intake
10. Sedentary life style
11. History of Chemotherapy or radiotherapy

Who is At Risk?

Current myocardial disease

1. Heart failure (with either preserved or reduced ejection fraction)
2. Asymptomatic LV dysfunction (LVEF less than 50% or elevated BNP)
3. Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischemia)
4. Moderate and severe VHD with LVH or LV impairment
5. Hypertensive heart disease with LV hypertrophy
6. Hypertrophic cardiomyopathy, Dilated cardiomyopathy , Restrictive cardiomyopathy
7. Cardiac sarcoidosis with myocardial involvement

When and how frequent should I screen for myocardial damage?

1. Base line before initiation of treatment.
2. Follow up during chemotherapy is set according to the type of chemotherapy and the risk factors of the patient
3. Follow up after completion of treatment
4. In high risk patients (high doses of anthracycline & who developed myocardial dysfunction) long term follow up should be implemented upto 5 years in certain cases

How should we screen for LV dysfunction??

Echocardiography

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: - 3D-based LVEF - 2D Simpson's LVEF - GLS	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.

Nuclear Cardiac imaging

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Nuclear cardiac imaging (MUGA)	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures.

Cardiac magnetic resonance

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).

LAB

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Cardiac biomarkers: - Troponin I - High-sensitivity Troponin I - BNP - NT-proBNP	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

Proposed diagnostic tools for the detection of cardiotoxicity

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Key points

- lower limit of normal of LVEF in echocardiography is 50%.
- A patient with a significant decrease in LVEF (e.g. a decrease more than10%), to a value that does not drop below the lower limit of normal, should undergo repeated assessment of LVEF shortly after and during the duration of cancer treatment.
- If LVEF decreases more than10% to a value below the lower limit of normal (considered as an LVEF ,50%), ACE inhibitors (or ARBs) in combination with beta-blockers are recommended.

Coronary artery disease

- Myocardial ischemia is a side effect of several cancer therapies. The mechanisms by which these drugs cause myocardial ischemia are diverse .

1. Direct vasospasm
2. Endothelial injury
3. Acute arterial thrombosis
4. Long-term changes in lipid metabolism and consequent premature arteriosclerosis

Pathophysiological mechanisms of coronary artery disease in cancer treatment

Agent	Pathophysiological mechanism	Risk of coronary artery disease and acute coronary syndrome
Fluoropyrimidines (5-FU, capecitabine, gemcitabine)	• Endothelial injury • Vasospasm	• Up to 18% manifest myocardial ischaemia • Up to 7–10%: silent myocardial ischaemia
Platinum compounds (cisplatin)	• Procoagulant status • Arterial thrombosis	• 20-year absolute risk of up to 8% after testicular cancer • 2% risk of arterial thrombosis
VEGF inhibitors (bevacizumab, sorafenib, sunitinib)	• Procoagulant status • Arterial thrombosis • Endothelial injury	• Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, sunitinib 1.4%
Radiotherapy	• Endothelial injury • Plaque rupture • Thrombosis	• 2–7-fold increased relative risk of myocardial infarction • Cumulative 30-year coronary events incidence of 10% in Hogdkin lymphoma survivors • Risk proportional to irradiation dose

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Key points

1. Patients treated with pyrimidine analogues (5FU) should be closely monitored for myocardial ischemia using regular ECGs, and chemotherapy should be withheld if myocardial ischemia occurs.
2. Reinitiating chemotherapy after coronary vasospasm should be reserved for when no other alternatives exist, and only under prophylaxis(calcium blockers and nitrates) and close monitoring of the patient.
3. Long-term clinical follow-up and testing for the presence of CAD may be useful to identify patients with cardiac disease who develop long-term complications of chemotherapy and radiotherapy.

Thank you