CARDIOVASCULAR TOXICITY OF ANTICANCER TREATMENT

Yousery Wasef Nada
MD medical oncology
Head of medical oncology department
Maadi armed forces medical compound

- Cardiooncology, what, why and who?
- Myocardial dysfunction and heart failure.
- Cardio-toxicity of anti-cancer agents(type I vs type II).
- Anthracycline induced cardio toxicity.
- Trastuzumab associated cardiotoxicity.
- Cardiac ischemia.
- Rhythm Disturbances and QTc Prolongation.
- Hypertension.
- Thromboembolic disease.
- Cardiotoxicity induced by radiotherapy.
- Diagnostic tools for detection of cardiotoxicity.
- ESMO guidelines for monitoring and treatment

WHAT IS THE CARDIO-ONCOLOGY ?
(THE CARDIOVASCULAR CARE OF CANCER PATIENTS)

- **Cardio-oncology is an inclusive discipline focused on the cardiovascular health of cancer patients and cancer survivors**.

WHY CARDIO-ONCOLOGY ?

Advances in treatment have led to improved survival of patients with cancer, but have also increased morbidity and mortality due to treatment side effects.

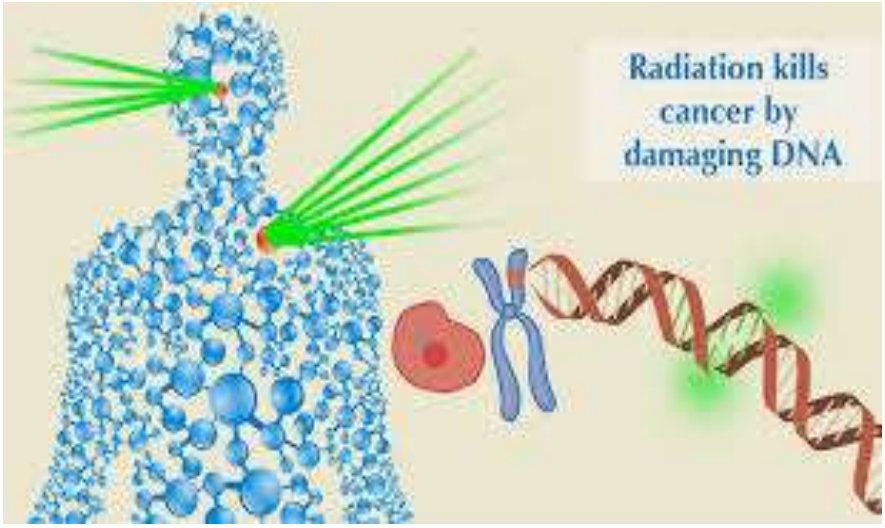
Cardiovascular diseases (CVDs) are one of the most frequent of these side effects, and there is a growing concern that CVDs may lead to premature morbidity and death among cancer survivors.

WHO IS A CARDIO-ONCOLOGIST ?

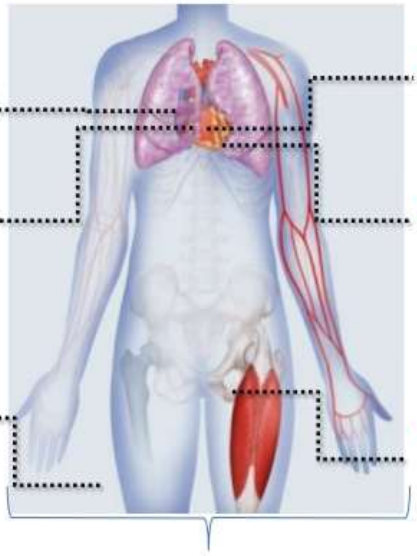
-A cardio-oncologist is a health care provider who is focused on the prevention, early detection, and management of, and recovery from, cardiac injury that may stem from cancer or cancer therapies.

TARGETED THERAPY

RADIOTHERAPY



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

MYOCARDIAL DYSFUNCTION AND HEART FALIURE

TYPE I AND TYPE II TREATMENT-RELATED CARDIAC DAMAGE

Type I	Type II
Doxorubicin is the model	Trastuzumab is the model
Direct myocyte death	Myocyte dysfunction
Permanent myocyte injury, beginning from first dose (Irreversible)	Reversible myocyte dysfunction, with favourable prognosis
-Vacuole formation -Myofibril disarray -Necrosis	Minimal changes have been reported; none of the characteristic changes of the type I agents are seen
Cumulative dose-related effect	No cumulative dose-related effect noted
-Any condition that has damaged or strained the myocardium -Genetic sensitivity to these agents	-Prior recent exposure to anthracyclines ((trastuzumab) -Hypertension (sunitinib) -Tendency to retain fluid (imatinib) -Genetic sensitivity*

INCIDENCE OF LEFT VENTRICULAR DYSFUNCTION (LVD) AND HEART FALIURE(HF) WITH CHEMOTHERAPY(TYPE I)

Chemotherapy agents		Incidence(%)
Anthracyclines:		
- Doxorubcine (Adriamycin) .		3-5% (400mg / m²) 7-26% (550 mg /m²) 18-48% (700mg/ m²)
- Epirubicin (Farmarubicin)		0.5- 11.4% (>900mg/m²)
- Mitoxantrone (Novantrone)		2.6% (>120mg /m²)
Alkylating agents:		
-Cyclophosphamide(Endoxan)		7-28%
-Ifosfamide (Holoxan)	<10g/ m² 12.5-16g/ m²	0.5% 17%
Antimicrotubule:		
-Paclitaxel(Taxole)		<1%
-Docetaxel(Taxoter)		2.3-13%

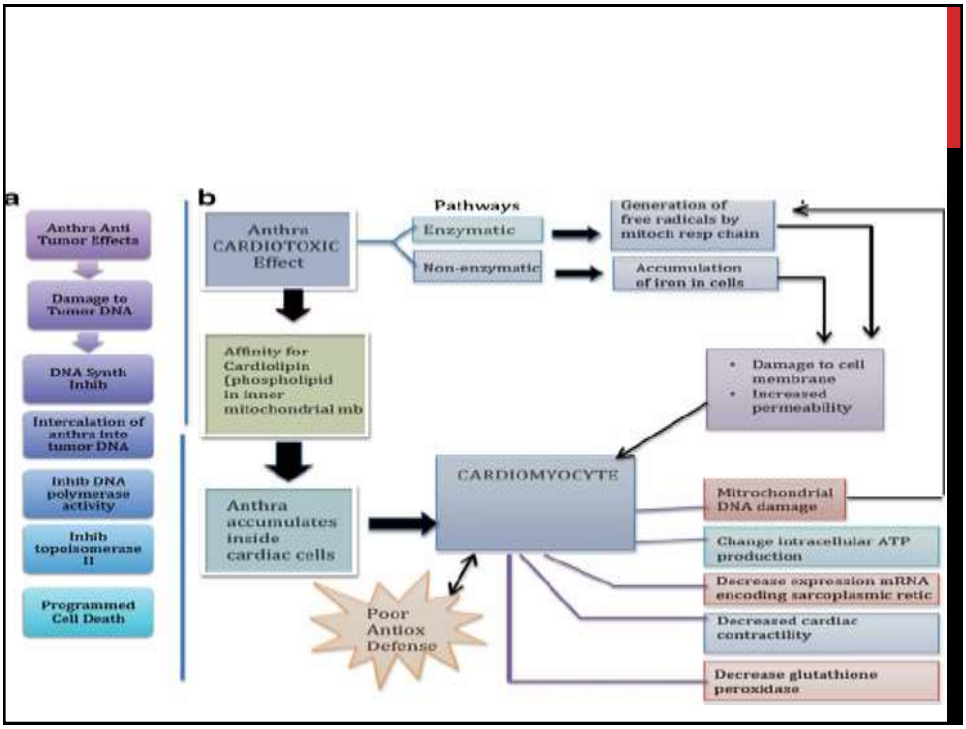
CLINICAL PRESENTATION OF ANTHRACYCLINE INDUCED CARDIOTOXICITY

- **Acute cardiotoxicity :**
  - In < 1% of patients.
  - Immediately after infusion of anthracycline .
  - Acute , transient decline in myocardial cotractility.
  - Reversible.
- **The early onset chronic progressive form:**
  - In 1.6%-2.1% of patients.
  - During therapy or within the first year after treatment.
  - Dilated CMP& LV dysfunction& HF.
  - Irreversible.
- **Late onset chronic progressive form:**
  - In 1.6%- 5% of patients.
  - At least 1 year after completion of therapy(10-20 years).
  - Dilated CMP& LV dysfunction& HF.
  - Irreversible.

RISK FACTORS FOR ANTHRACYCLINE INDUCE CARDIOTOXICITY

- **Treatment related:**
  - Cumulative dose of anthracycline.
    . Doxorubicine……..400-550 mg/ m^2.
    .Epirubicin……..900 mg/ m^2
  - Dosing schedule
  - Method of administration (rapid IV adminestration)
  - Radiation therapy.
  - Co-administration of additional potentially cardiotoxic agents.

- **Patient related**
  - Age.
    .>65 years old.
    . Pediatric population(<18 years)
  - Female
  - Pre-existing CV disease or cardiac risk factors
    (Hypertension, DM, Hypercholesterolaemia, obesity and smoking).
  - Genetic factors



INCIDENCE OF LEFT VENTRICULAR DYSFUNCTION (LVD) AND HEART FALIURE(HF) WITH TARGETED THERAPY (TYPE II)

Targeted Therapy	Incidence
Monoclonal antibody:	
- Trastuzumab (Herceptine)	1.7-27.1%
- Bevacizumab (Avastine)	1.6-4%
- Pertuzumab (Perjeta)	0.7-1.2%
Small molecule TKIs:	
- Sunitinb(Sutient)	2.7-19%
- Pazopanib (Votrient)	7-11%
- Sorafenib (Nexavar)	4-8%
- Imatinib mesylate (Glivic)	0.2- 2.7%

TRASTUZUMAB ASSOCIATED CARDIOTOXICITY(TYPE II)

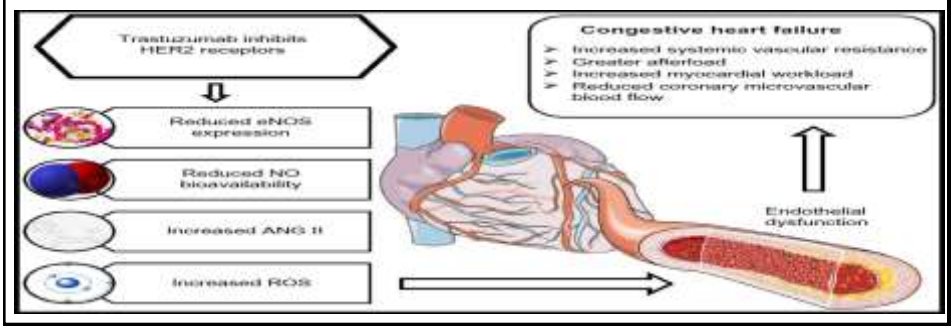
Metastatic BC	Non metastatic BC
Monotherapy…….2%-7%	
With paclitaxel….2%-13%	
With anthracycline…27%	

CARDIOTOXICITY REPORTED IN MAJOR ADJUVANT TRASTUZUMAB TRIALS

Trial	Time interval between anthracycline and trastuzumab	Reported incidence of CHF (%)	Reported incidence of LV dysfunction (%)	Reversibility reported	Reported cardiac deaths (*n*)
FinHER[104]*	(Trastuzumab given prior to anthracycline)	0.9	6.8	Data not available	0
Slamon et al[61]‡	Concurrent	16	27	Yes	1
NSABP B-31[18]	21 days	4.0	Data not available	Yes	1
NCCTG N9831;[28] arm B	105 days	2.8	7.8	Yes	1
NCCTG N9831;[28] arm C	21 days	3.3	10.4	Yes	0
BCIRG-006;[29] anthracycline arm	21 days	2.0	18.6	Yes	0
BCIRG-006;[29] nonanthracycline arm	NA	0.4	9.4	Yes	0
HERA;[105§] 1-year arm	89 days	0.8	4.1	Yes	0

MECHNISM OF TRASTUZUMAB ASSOCIATED CARDIOTOXICITY(TYPE II)

- The precise pathophysiological mechanisms by which trastuzumab act on cells is not known,
- it is thought to be closely linked to inhibition of HER 2 cardiac signalling. Several studies have demonstrated the important role of HER2 in cardiomyocyte survival and development.



CARDIAC ISCHEMIA

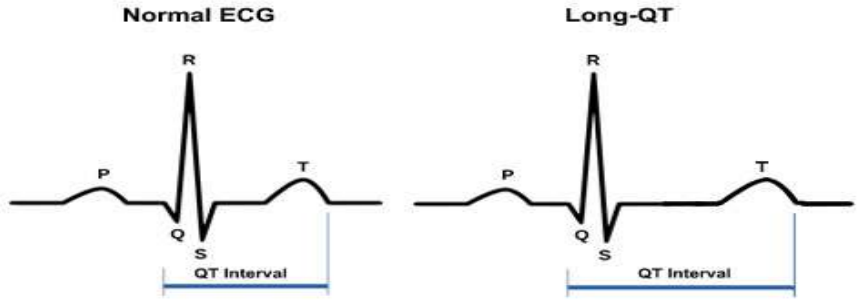
CARDIAC ISCHEMIA

Agent	Mechanism	Risk of ishemia
Antimetabolites: (5-FU, capecitabine, gemcitabine) **Microtubule inhibitors** Paclitaxel	• Endothelial injury • Coronary spasm. • Arteritis.	- 1%-68%. • 5%
Platinum compound: (cisplatin)	• Procoagulant status • Arterial throimbosis	-2% risk of arterial thrombosis. -20-year absolute risk of up to 8% after testicular cancer
VEGF inhibitors: (Bevacizumab, sorafenib, sunitinib)	• Procoagulant status • Arterial throimbosis • Endothelial injury	- Bevacizumab 3.8%. - Sorafaenib 1.7%. - Sunitinib 1.4%
Endocrine agents: (Aromatase inhibitors)	• Differential changes in lipid profile	• RR 1.31

ARRHYTHMIAS

RHYTHM DISTURBANCES AND QTC PROLONGATION

- Cancer therapies may be associated with a variety of rhythm disturbances but most notably can prolong the QT interval, potentially leading to ventricular arrhythmias.



CANCER DRUG ASSOCIATED WITH CARDIAC ARRHYTHMIAS

Type of arrhythmia	Causative drug
QT prolongation	Arsenic trioxide (ATO).....(TRISONIX) in treatmeni APL HDACI-TKIs- Doxorubicin.
Bradycardia	ATO- Pclitaxel- IL2.
Sinus tachycardia	Anthracyclines- Carmustine.
Atrioventricular block	Cyclophosphamide- Bortezomib- Anthracyclines.
Atrial fibrillation	Alkylating agents-Antimetabolites-VP16-IL2- Interferons-TKIs- Vinca alkaloids.
SVT	Alkylating agents-Antimetabolites-IL2- Porteasome inhibitors-Rituximab.
Ventricular tachycardia	Alkylating agents-Antimetabolites-IL2- Porteasome inhibitors-Rituximab.
Sudden cardiac death	Anthracyclines- ATO- 5FU- Interferons

HYPERTENSION

HYPERTENSION

- Hypertension is the most frequent cardiotoxicity observed with VEGF signaling pathway(VSP)inhibitors, with a reported incidence of 9% to 40%.
- **The mechanisms of hypertension induced by VSP inhibitors:**

1-Reduced nitric oxide production in the wall of arterioles.

2-Increased endothelin-1 production.

3-Capillary rarefaction that results in the reduction of effective capillary beds.

VSP INHIBITORS AND INCIDENCE OF HYPERTENSION

VSP Inhibitors	Incidence of hypertension
Bevacizumab	• CRC 34%. • Breast 24%. • RCC 6%. • GBM 30%
Pazobanib	• RCC 40%
Sorafenib	• RCC 17%. • HCC 9%.
Sunitinib	• RCC 30%. • GIST 15%

THROMBOEMBOLIC DISEASE

THROMBOEMBOLIC DISEASE

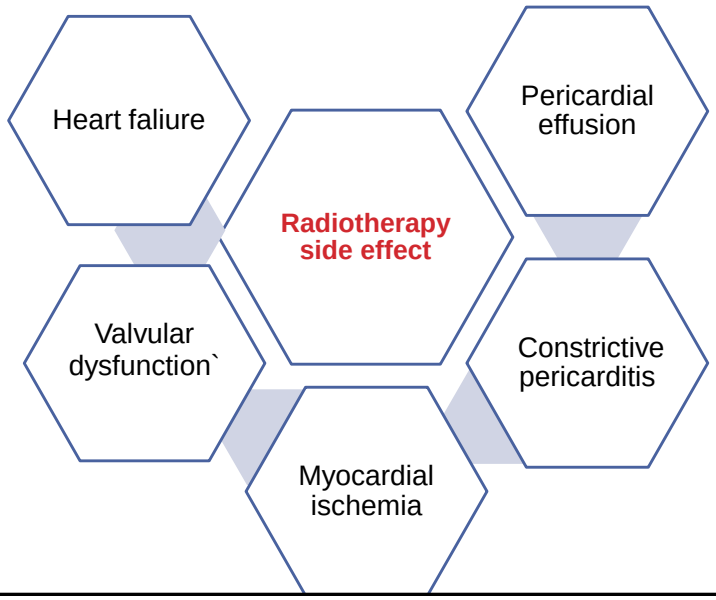
Arterial thrombosis

- 1%(rare).
- Metastatic pancreatic, breast, colorectal and lung cancer.
- Cancer therapies….VEGF inhibitors& Aromatase inhibitor.

Venous thrombosis

- 20% of hospitalized patients. (frequently underrecognized)
- Bladder, colon, lung, stomach and pancreatic cancer.
- Cancer therapy…….Tamoxifen &Thalidomide

CARDIAC TOXICITY INDUCED BY RADIOTHERAPY



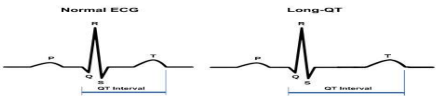
DIAGNOSTIC TOOLS FOR DETECTION OF `CARDIOTOXICITY

DIAGNOSTIC TOOLS FOR DETECTION OF CARDIOTOXICITY

- Electrocardiography.
- Echocardiography.
- Nuclear cardiac imaging
  (Multigated acquisition scans (MUGA scan).
- Cardiac magnetic resonance (CMR).
- Cardiac biomarkers:
  -Troponin I .
  - High-sensitivity Troponin I.
  - B-type natriuretic peptide (BNP).
  - NT-proBNP.

ELECTROCARDIOGRAPHY(ECG)

- ECG is recommended in all patients before and during treatment.
- Can detect any ECG signs of cardiac toxicity:
  - Resting tachycardia.
  - ST-T wave changes.
  - QT interval prolongation.
  - Arrhythmias.



- Not specific and can be related to other factors.

ECHOCARDIOGRAPHY
(TRANSTHORACIC ECHOCARDIOGRAPHY)

- **Commonly used either as an alternative imaging modality for serial assessment of LVEF in patients with cancer or as confirmation of a poor LVEF detected by MUGA.**

- **Advantage:**

  -Wide availability.

  - Lack of radiation.

  -Assessment of haemodynamics and other cardiac structures.

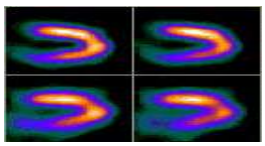
- **Major limitations:**

  -Inter-observer variability.

  -Image quality

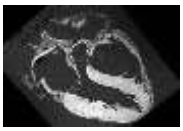
  -No considerable change in LVEF occurs until a critical amount of myocardial damage.

NUCLEAR CARDIAC IMAGING
(MITIGATED ACQUISITION SCANS (MUGA SCAN).



- **The MUGA scan is performed by labeling the patient's red blood pool with a radioactive tracer, technetium 99m-pertechnetate(Tc-99m), for determining LVEF.**
- **Advantage:**
  - **MUGA is preferred for patients with poor windows on echo-cardiography(e.g. obesity)**
  - **Reproducibility.**
  - **Low interobserver and intraobserver variability**
- **Major Limitation:**
  - **Cumulative radiation exposure.**
  - **Limited structural and functional information on other cardiac structure.**
  - **Inaccurate in many situations (Arrhythmias, drugs)**
  - **Costly**

CARDIAC MAGNETIC RESONANCE(CMR)



- **Magnetic resonance imaging (MRI) is considered the gold standard for the evaluation of LV volumes , mass and function.**
- **Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderline.**

- **Advantage:**
  - **Accuracy , reproducibility.**
  - **Detection of diffuse myocardial fibrosis usingT1/T2 mapping.**
- **Major limitation:**
  - **Limited availability.**
  - **Patient´ adaptation.**

CARDIAC BIOMARKERS

Troponins:

- Cardiac troponins are regulatory proteins within the myocardium that are released into the circulation when damage to the myocyte has occurred.
- Strong data indicate that troponin detects anticancer drug induced-cardiotoxicity in its earliest phase, long before any reduction in LVEF has occurred.

- **Measurement of troponins may provide additional information,including:**

1. Prediction of the severity of future LVD, because the peak value of troponin after chemotherapy is closely correlated to the extent of LVEF reduction;
2. Stratification of cardiac risk after chemotherapy, which allows for the personalization of the intensity of post chemotherapy monitoring of cardiac function;
3. Selection of patients more prone to develop cardiotoxicity,in whom cardioprotective therapy can be considered;
4. Exclusion of most patients from prolonged cardiologic monitoring.

- **High-sensitivity troponins:**

  -These new high sensitivity (HS) assays can now reliably measure small increases that are undetectable by using other troponin assays.

- **Natriuretic peptides (BNP &NT- pro BNP):**

  - Increased NP levels can detects chemotherapy –induced LVD in both adults and pediatric populations.
  - Many studies failed to find a correlation between the increase in NP and the development of cardiac dysfunction.
  - New prospective and multicenter studies using well standardized methods for dosage. Well defining timing of sampling and cardiac end points are paramount to clarify the appropriate use of NP.

Limitation of cardiac biomarkers:

- **Insufficient evidence to establish the significance of subtle rises.**
- **Variations with different assays.**
- **Role for routine surveillance not clearly established.**

CV MONITORING DURING AND AFTER ANTICANCER TREATMENT WITH POTENTIAL NON-REVERSIBLE (TYPE I) OR REVERSIBLE (TYPE II) CARDIOTOXICITY (ESMO GUIEDLINE)

Guideline statements	Level of evidence	Grade of recommendation
- Patients receiving anthracyclines and/or trastuzumab in the adjuvant setting should perform serial monitoring of cardiac function at baseline, 3, 6 and 9 months during treatment, and then at 12 and 18 months after the Initiation of treatment. Monitoring should be repeated during or following treatment as clinically indicated..	I	A
- Patients treated for metastatic disease: LVEF should be monitored at baseline and then infrequently in the absence of symptoms.	II	A
-Troponin I or BNP concentrations seem to identify patients at risk of cardiotoxicity, specifically in case of administration of type I agents (such as anthracyclines). Performing baseline assessment of biomarker concentrations and periodic measurements during therapy (every each cycle) may identify patients who need further cardiac assessment.	III	B

-Assessment of cardiac function is recommended 4 and 10 years after anthracycline therapy in patients who were treated at <15 years of age, or even at age >15 years but with cumulative dose of doxorubicin of >240 mg/m2 or epirubicin >360 mg/m2 .	II	B
-LVEF reduction of ≥15% from baseline with normal function (LFEV ≥ 50%) is an indication to continue anthracyclines and/or trastuzumab. LVEF decline to <50% during anthracyclines containing regimens necessitate reassessment after 3 weeks. If confirmed, hold chemotherapy, consider therapy for LVD and further frequent clinical and echocardiographic checks. In case of LVEF decline to <40% stop chemotherapy, discus alternatives and treat LVD.	II	B

-LVEF decline to <50% during trastuzumab therapy (post-anthracyclines) necessitate reassessment after 3 weeks. -If confirmed, continue trastuzumab and consider therapy for LVD and further frequent clinical and echocardiographic checks. -In case of LVEF decline to <40% stop trastuzumab and treat LVD -Aggressive medical treatment of those patients, even asymptomatic, who show LVD at DEcho after anthracycline Therapy is mandatory, especially if the neoplasia could have a long-term survival; it consists of ACE inhibitors and b-blockers and the earlier HF therapy is begun (within 2 months from the end of anthracycline therapy), the better the therapeutic response		

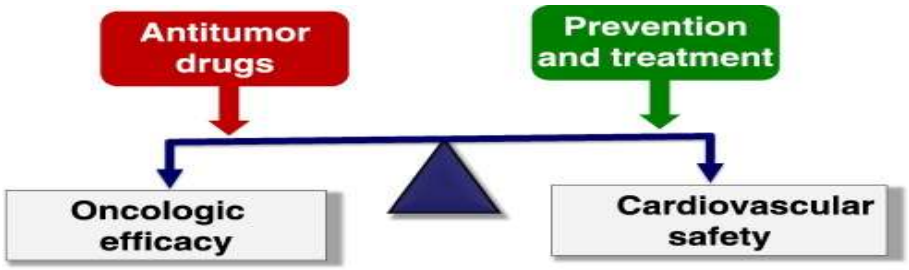
TREATMENT OF LVD INDUCED BY ANTICANCER TREATMENT WITH NON-REVERSIBLE (TYPE I) OR REVERSIBLE (TYPE II) CARDIOTOXICITY (ESMO GUIEDLINE)

Guideline statements	Level of evidence	Grade of recommendation
- In patients with subclinical cardio toxicity induced by Type1 agents, identified also by increase in cardiac troponin, a treatment with ACE inhibitors (enalapril) may prevent LVEF reduction and associated cardiac events. - Patients who develop cardiac dysfunction during or following treatment with Type II agents (trastuzumab) in the absence of anthracyclines can be observed if they remain asymptomatic and LVEF remains ≥40 . - Persistently low or further declines in LVEF or development of symptoms should trigger discussion of risk and benefit with he treating oncologist, as well as consideration for pharmacologic cardiac treatment. HF therapy just as any other HF	II	A
- Patients who develop LVD should be treated with standard guideline-based HF therapy just as any other HF therapy just as any other HF patient.	II	A

*Take home message

- **A thoughtful risk management plan generated by an organized collaboration between oncologist , cardiologist and regulatory agencies can support development programs essential for anticancer agents with cardiac safety concerns.**

- **A crucial balance exists between reducing cardiac events related to cancer treatment while striving to provide optimal antitumor efficacy.**




L
Thank You