Cardiac toxicity of cancer therapy

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Cardiovascular characteristics of cancer survivors

1- Increased prevalence of conventional CVD risk factors

2- Incidence of second primary neoplasm

3- Incidence of viral myocarditis due to prolonged immune suppression (EB, CMV, Herpes)

5- Incidence of DVT, PE

6- Cardiac toxicity of cancer treatment

Cardiovascular Toxicity of Selected Chemotherapy Agents

Heart Failure	Hypertension	Acute Coronary Syndromes	QTc Prolongation
Anthracyclines Trastuzumab Lapatinib Alemtuzumab	Bevacizumab Sorafenib Sunitinib VDAs*	Fluorouracil Bevacizumab Sorafenib VDAs	Arsenic trioxide Depsipeptide Sunitinib Dasatinib VDAs

*Vascular disrupting agents
Source: Dr. Nohria

- **Incidence of cardiac toxicity varies widely**
- **Thorough knowledge of the agent(s) used is esential**

Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m² 550 mg/m² 700 mg/m²	 3–5 7–26 18–48
Idarubicin (>90 mg/m²)	5–18
Epirubicin (>900 mg/m²)	0.9–11.4
Mitoxanthone >120 mg/m²	2.6
Liposomal anthracyclines (>900 mg/m²)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m² 12.5–16 g/m²	 0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7–20.1[26a]
Bevacizumab	1.6–4[14b]
Pertuzumab	0.7–1.2

Types of cardio-toxicity

Type I (permanent damage) anticancer agents

- Doxorubicin (anthracycline)
- Daunorubicin (anthracycline)
- Epirubicin (anthracycline)
- Idarubicin (anthracycline)
- Mitoxantrone (anthracenedione)
- Cyclophosphamide (oxazophorine alkylating agent)

Type II (reversible damage) anticancer agents

- Trastuzumab (monoclonal antibody)
- Sunitinib (tyrosine kinase inhibitor)
- Lapatinib (tyrosine kinase inhibitor)

Baseline risk factors

Current myocardial disease	*Demographic and other CV risk factors*
• Heart failure (with either preserved or reduced ejection fraction) • Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide[a]) • Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia) • Moderate and severe VHD with LVH or LV impairment • Hypertensive heart disease with LV hypertrophy • Hypertrophic cardiomyopathy • Dilated cardiomyopathy • Restrictive cardiomyopathy • Cardiac sarcoidosis with myocardial involvement • Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias)	• Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for anthracyclines) • Family history of premature CV disease (<50 years) • Arterial hypertension • Diabetes mellitus • Hypercholesterolaemia

Baseline risk factors (cont)

Previous cardiotoxic cancer treatment	*Lifestyle risk factors*
• Prior anthracycline use • Prior radiotherapy to chest or mediastinum	• Smoking • High alcohol intake • Obesity • Sedentary habit

Radiation

- Measurement units
  Gray unit (Gy)= 1Kcal delivered to 1Kg mass
- Risk factors:
- Dose
- amount of exposed cardiac tissue
- duration of survival
- CVD risk factors
- concomitant or preceding chemotherapy.
- Common in:
- breast cancer
- mediastinal lymphoma
- bone marrow transplantation

Valve disease

Atherosclerosis
(Symptomatic or asymptomatic)

Pericardial disease
(Acute pericarditis; chronic pericarditis; pericardial effusion; constrictive pericarditis)

Myocardial and endocardial disease
(Pancarditis, cardiomyopathy)

Conduction disturbances
(Right bundle branch block, atrioventricular block)

Table 2 Factors associated with risk of cardiotoxicity following treatment with anthracyclines[a]

Risk factors
• Cumulative dose • Female sex • Age - >65 years old - Paediatric population (<18 years) • Renal failure • Concomitant or previous radiation therapy involving the heart • Concomitant chemotherapy - alkylating or antimicrotubule agents - immuno- and targeted therapies • Pre-existing conditions - Cardiac diseases associating increased wall stress - Arterial hypertension - Genetic factors

Table 2

Strategies for Preventing Anthracycline-Induced Cardiotoxicity

Strategies	Description/Effects	References
Administration schedule	Prolonged infusion can reduce cardiotoxicity	40-42
Liposomal formulation	Can reduce cardiotoxicity without compromising efficacy	43-45
Cardioprotectant	Dexrazoxane is the only FDA-approved drug, use is limited to women with metastatic breast cancer	46-47
ACEIs/ARBs	Prevent progression of LV dysfunction, may reduce cardiotoxicity if given concurrently with anthracycline	48-50
Coenzyme Q10	More studies are underway to evaluate its cardioprotective effect	51-54

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocking agent; FDA = US Food and Drug Administration; LV = left-ventricular.

Anthracyclins

Monitoring :

LVEF, troponin, BNP

LVEF: MUGA vs. Echo

Guidelines :

1. **Baseline EF >50% start monitoring at 300 mg/m2. At least 3w after each dose. D/C if EF ⬇>20% or to <50%**
2. **Baseline EF 50-31% start monitoring at 100 mg/m2. D/C if EF ⬇>10% or to 30% or less.**
3. **Baseline EF <31% Do not start anthracyclins.**

Tools for monitoring cardiac toxicity

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 (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.

Monitoring according to cumulative anthracycline dose

Anthracycline cumulative dose (mg/m^2*)	Pre-treatment	During treatment	At end of treatment	First year following treatment	Years 2–5 following treatment	>Year 5 following treatment
<200	Yes	As clinically indicated	Yes	Follow-up at 1 year	Follow-up at 2 years and at 5 years	As clinically indicated
200–300	Yes	After 200 mg/m^2	Yes	Follow-up at 6 months and at 1 year	Follow-up at 2 years, 3 years and at 5 years	As clinically indicated
300–400	Yes	After 200, 300 and 350 mg/m^2	Yes	Follow-up at 6 months and at 1 year	Follow-up annually	Follow-up every 2 years
>400	Yes	After 200, 300, 350 and 400 mg/m^2	Yes	Follow up at 3 months, 6 months and at 1 year	Follow-up annually	Follow-up annually

*Cumulative doses are given for doxorubicin; for mitoxantrone multiply dose by 0.2, for epirubicin and liposomal preparations multiply dose by 1.5.

Balancing cardiac risk & oncologic benefit

Potential cardiac risk	Potential oncologic benefit		
	High	Intermediate	Uncertain or low
Low (no risk factors*)	Standard monitoring	Use with caution; consider non-anthracycline regimens	Consider non-anthracycline regimens
Moderate (1–2 risk factors)	Consider increased monitoring; consider cardioprotective regimens	Use with caution; consider increased cardiac monitoring; consider cardioprotective regimens	Avoid anthracyclines
High (>2 risk factors)	Use with extreme caution; consider cardioprotective regimens	Avoid anthracyclines	Avoid anthracyclines

*Risk factors include planned cumulative doxorubicin dose of >300 mg/m^2 or equivalent, age >65 years, hypertension, coronary artery disease, other cardiac disease, and cardiac irradiation.

Non-anthracyclins

Cyclophosphamide

- potentiates cardiac toxicity of anthracyclins and radiotherapy.
- Isolated therapy is minimally cardiotoxic.

Thiouracil

- Coronary artery spasm, MI.
- Amlodipine treatment of choice.

Paclitaxel

- Potentiates toxic effect of TRASTOZUMAB.
- Minimal toxicity alone.

Targeted therapy

TRASTOZUMAB (HERCEPTIN)

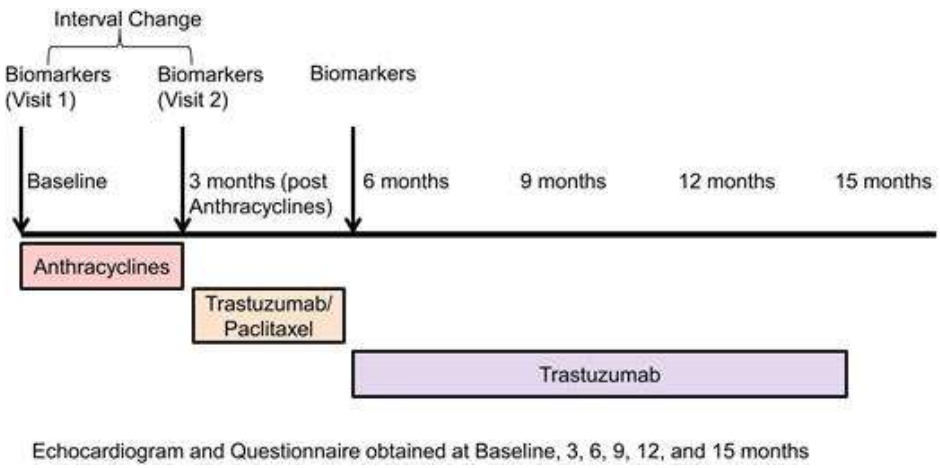
For metastatic HER positive breast cancer.
Usually given in weekly doses for 6 months

CHF 5-10%

- low fatality
- largely reversible
- Not potentiated by radiotherapy.

Risk factors :

- Age>50
- HTN
- obesity,
- baseline LV dysfunction
- concomitant Paclitaxel.



Echocardiogram and Questionnaire obtained at Baseline, 3, 6, 9, 12, and 15 months

Risk factors for Anti-HER2 toxicity

Anti-HER2 compounds	
- Antibodies - Trastuzumab - Pertuzumab - T-DM1 - Tyrosine kinase inhibitor - Lapatinib	• Previous or concomitant anthracycline treatment *(short time between anthracycline and anti-HER2 treatment)* • Age (>65 years) • High BMI >30 kg/mg^2 • Previous LV dysfunction • Arterial hypertension • Previous radiation therapy

Risk factors for VEGF inhibitor toxicity

VEGF inhibitors	
- Antibodies - Bevacizumab - Ramucirumab	Pre-existing HF, significant CAD or left side VHD (e.g. mitral regurgitation), chronic ischaemic cardiomyopathy • Previous anthracycline
- Tyrosine kinase inhibitors - Sunitinib - Pazopanib - Axitinib - Neratinib - Afatinib - Sorafenib - Dasatinib	• Arterial hypertension • Pre-existing cardiac disease

Key message

1. Cancer patients treated with potentially cardiotoxic therapy are at high risk of developing HF and should receive medical care for strict control of cardiovascular risk factors.
2. LVEF should be determined before and periodically during treatment for early detection of cardiac dysfunction in these patients, with a method that provides sufficient image quality and using the same method during follow-up.
3. The lower limit of normal of LVEF in echo is 50%, in line with the definition of cardiotoxicity commonly used in registries and trials.

4. With a significant decrease in LVEF (>10%), to a value not below the lower limit of normal, repeated assessment of LVEF is needed shortly after and during the duration of cancer treatment.

5. If LVEF decreases >10% to a value below the lower limit of normal, ACEI (or ARBs) with BB are recommended to prevent further LV dysfunction or the development of symptomatic HF, unless contraindicated.

6. ACEI (or ARBs) and BB are recommended in patients with symptomatic HF or asymptomatic cardiac dysfunction unless contraindicated.