Cancer treatment in cardiac patient

case based presentation

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ESC CPG POSITION PAPER

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The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

- 42 years old female
- Discovered **ASD** at the age of 15Years
- At the age of 25 years after the 1st delivery she had CHF NYHA III and syncope
- She had surgical closure of ASD with stabilization of symptoms and residual grade 1 diastolic dysfunction and **normal EF**
- Last year she was discovered to have **non Hodgkin's lymphoma** after severe Abdominal pain

Does this patient has a baseline risk for cardio-toxicity?

A. Yes

B. No

Does this patient has a baseline risk for cardio-toxicity?

A. Yes

B. No

Table 4 Baseline risk factors for cardiotoxicity

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

Breast Cancer Res Treat. 2011 Dec;130(3):845-54. doi: 10.1007/s10549-011-1714-9. Epub 2011 Sep 15.

Baseline diastolic dysfunction as a predictive factor of trastuzumab-mediated cardiotoxicity after adjuvant anthracycline therapy in breast cancer.

Cochet A[1], Quilichini G, Dygai-Cochet I, Touzery C, Toubeau M, Berriolo-Riedinger A, Coudert B, Cottin Y, Fumoleau P, Brunotte F.

⊕ Author information

Abstract

To evaluate the interest in assessing left ventricular diastolic function at baseline for prediction of trastuzumab-mediated cardiotoxicity (TMC) in the setting of adjuvant treatment for breast cancer. The study included 118 women presenting with HER2-positive early-stage invasive breast cancer. Patients received trastuzumab therapy over 1 year, concurrent with six cycles of docetaxel (n = 53), or following anthracycline-based chemotherapy with a cumulative dose of 300 mg/m(2) (n = 45) or 600 mg/m(2) (n = 20) of epirubicine. RNA was performed before anthracycline-based chemotherapy, before trastuzumab treatment (baseline), and every 3 months during treatment. Left ventricular ejection fraction (LVEF) and peak ejection rate (PER) were calculated to evaluate LV systolic function; peak filling rate (PFR), and time to peak filling rate (TPFR) were also calculated to evaluate LV diastolic function. Eighteen patients (15%) developed grade 1 or 2 TMC during follow-up. No significant difference was observed for age, cardiovascular risk factors, fasting blood glucose level, heart rate, systolic blood pressure, baseline LVEF, PER, and PFR between patients with and without TMC. In contrast, patients with TMC showed a longer TPFR at baseline (median [Q1-Q3]: 165 ms [149-190] vs. 142 ms [130-162]; P < 0.001). Furthermore, by logistic regression analysis, baseline TPFR >180 ms and the cumulative dose of epirubicin remained independent predictors of TMC. Patients receiving 600 mg/m(2) of epirubicin before trastuzumab showed a higher incidence of TMC (35%) than did both patients who previously received 300 mg/m(2) of epirubicin (13%) and those who received only docetaxel associated with trastuzumab (9%). Impaired left ventricular diastolic function before treatment is an independent predictor of trastuzumab-mediated cardiotoxicity. The evaluation of diastolic function could allow optimal risk stratification before the introduction of trastuzumab.

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[PubMed - indexed for MEDLINE]

- Treatment with (RCHOP) chemotherapy was indicated
- She had **one** echocardiography revealed within normal LVEF and Grade I diastolic dysfunction
- There was no other echocardiography evaluation during the treatment
- **RCHOP**:
  R- rituximab
  C- cyclophosphamide
  H- doxorubicin (hydroxydaunomycin) (**400mg/m²)**
  O- vincristine (Oncovin®)
  P- prednisolone

Anthracyclins

Members: doxo, dono, epirubicin.

CHF up to 30% 5-10% fatal

Weeks to > 1 year after Rx.

Risk factors : cumulative dose, age, preexisting heart disease, concomitant cyclophosphamide or thiouracil, concomitant radiotherapy

Risk reduction : dose limitation, avoid concomitant radiotherapy, dextrazoxane, liposomal, (epirubicin less cardiotoxic). BB. ACEI. Statins. Monitoring.

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.

Small molecule cardiotoxicity

Cancer therapeutic classification	Commonly observed cardiotoxicities[a]
Tyrosine kinase inhibitors	• Hypertension • Vascular disease (including coronary artery, cerebrovascular, and peripheral arterial disease) • Arrhythmias (including atrial fibrillation) • QT prolongation • Cardiomyopathy/heart failure • Metabolic abnormalities (hyperlipidemia, hyperglycemia)
Proteosome inhibitors	• Hypertension • Cardiomyopathy/heart failure
Immunomodulating drugs	• Venous thromboembolism • Arterial thromboembolism (including myocardial infarction and stroke)
Immunotherapies/ checkpoint inhibitors	• Myocarditis • Arrhythmias (including atrial fibrillation) • Myocardial ischemia • Hypotension

Is there any change in patients risk?

A. Yes

B. No

Is there any change in patients risk?

A. Yes

B. No

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

[a]Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin) or anthracenedione (mitoxantrone).

Table 1 Incidence of left ventricular dysfunction associated with chemotherapy drugs[10–21]

Chemotherapy agents	Incidence (%)
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
Monoclonal antibodies	★
Trastuzumab	1.7–20.1[26]
Bevacizumab	1.6–4[16]
Pertuzumab	0.7–1.2

Do we need more surveillance of LVEF during treatment course?

A. Yes

B. No

Do we need more surveillance of LVEF during treatment course?

A. Yes

B. No

What do you suggest?

A. Clinical evaluation every cycle
B. Echocardiography every cycle
C. Cardiac MRI
D. Cardiac biomarkers
E. Combination of methods

What do you suggest?

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Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

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.
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).
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.

ACE-Is = angiotensin converting enzyme inhibitors; BNP = B-type natriuretic peptide; ECVF = extracellular volume fraction; GLS = global longitudinal strain; LV = left ventricular; LLN = lower limit of normality; LVEF = left ventricular ejection fraction; MUGA = multigated radionuclide angiography; NT-proBNP = N-terminal fragment B-type natriuretic peptide.

Anthracycline therapy

	High risk patient/ high dose	Regular therapy
LVEF assessment	An initial assessment in all patients	
	• **An assessment in a total** doxorubicin (or equivalent) dose of **240 mg/m²** • At 1 and 5 years for survivors with cardiotoxicity or had high dose **≥300 mg/m2**	At the end of treatment
Cardiac biomarkers	▪ Measurement of at least one cardiac biomarker may be considered at baseline ▪ **determination of (high-sensitivity troponin I) has been suggested with each cycle of anthracycline-containing chemotherapy.**	

Anti-HER2 therapy

	High risk patient/ high dose	Regular therapy
LVEF assessment	• An initial assessment in all patients specially those with adjuvant anthracycline administration • Cardiac monitoring is performed every 3 months during and once after completion of anti-HER2 treatment • early detection of LVEF decrease when troponins and speckle tracking echocardiography are used every 3 months during adjuvant trastuzumab treatment.	
Cardiac biomarkers	measurement of **troponin** with every cycle may be considered in patients with high baseline risk.	

VEGF inhibitors therapy

Some patients develop decrease in LVEF early and some develop it late

	High risk patient/ high dose	Regular therapy
LVEF assessment	• An initial assessment in all patients • Periodic echocardiography, for example, every 6 months until stability in LVEF values is achieved.	
	clinical follow-up in the first 2–4 weeks after starting targeted molecular therapy with	
Cardiac biomarkers	▪ every 2–3 months estimation of troponin or N-terminal pro-B-type natriuretic peptide (NT-proBNP)	

Can we prevent this risk?

A. Yes

B. No

Can we prevent this risk?

A. Yes

B. No

Table 13 Strategies to reduce chemotherapy-induced cardiotoxicity[226–228,245–248]

Chemotherapy drug	Potential cardioprotective measure
All chemotherapy drugs	Identify and treat cardiovascular risk factors
	Treat comorbidities (CAD, HF, PAD, HTN)
	QTc prolongation and torsade de pointes: - Avoid QT prolonging drugs - Manage electrolyte abnormalities
	Minimize cardiac irradiation
Anthracyclines and analogues	Limit cumulative dose (mg/m²): - Daunorubicin <800 - Doxorubicin <360 - Epirubicin <720 - Mitoxantrone <160 - Idarubicin <150
	Altered delivery systems (liposomal doxorubicin) or continuous infusions
	Dexrazoxane as an alternative
	ACE-Is or ARBs
	β-blockers
	Statins
	Aerobic exercise
Trastuzumab	ACE-Is
	β-blockers

ACE = angiotensin converting enzyme; ACE-I = angiotensin converting enzyme inhibitor; CAD = coronary artery disease; HF = heart failure; HTN = hypertension; PAD = peripheral artery disease; RCT = randomized controlled trial.

3.1.2 Patients with troponin elevation

Initiation of cardioprotection may be considered in patients with cancer who have a troponin increase during treatment with high-dose anthracycline-containing chemotherapy regimens.

Unfortunately this was not done!

J Am Coll Cardiol. 2013 Jun 11;61(23):2355-62. doi: 10.1016/j.jacc.2013.02.072. Epub 2013 Apr 10.

Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies).

Bosch X[*], Rovira M, Sitges M, Domènech A, Ortiz-Pérez JT, de Caralt TM, Morales-Ruiz M, Perea RJ, Monzó M, Esteve J.

Author information

Abstract

OBJECTIVES: This study sought to evaluate the efficacy of enalapril and carvedilol to prevent chemotherapy-induced left ventricular systolic dysfunction (LVSD) in patients with hematological malignancies.

BACKGROUND: Current chemotherapy may induce LVSD. Angiotensin-converting enzyme inhibitors and beta-blockers prevent LVSD in animal models of anthracycline-induced cardiomyopathy.

METHODS: In this randomized, controlled study, 90 patients with recently diagnosed acute leukemia (n = 36) or patients with malignant hemopathies undergoing autologous hematopoietic stem cell transplantation (HSCT) (n = 54) and without LVSD were randomly assigned to a group receiving enalapril and carvedilol (n = 45) or to a control group (n = 45). Echocardiographic and cardiac magnetic resonance (CMR) imaging studies were performed before and at 6 months after randomization. The primary efficacy endpoint was the absolute change from baseline in LV ejection fraction (LVEF).

RESULTS: The mean age of patients was 50 ± 13 years old, and 43% were women. At 6 months, LVEF did not change in the intervention group but significantly decreased in controls, resulting in a -3.1% absolute difference by echocardiography (p = 0.035) and -3.4% (p = 0.09) in the 59 patients who underwent CMR. The corresponding absolute difference (95% confidence interval [CI]) in LVEF was -6.38% (95% CI: -11.9 to -0.9) in patients with acute leukemia and -1.0% (95% CI: -4.5 to 2.5) in patients undergoing autologous HSCT (p = 0.08 for interaction between treatment effect and disease category). Compared to controls, patients in the intervention group had a lower incidence of the combined event of death or heart failure (6.7% vs. 22%, p = 0.036) and of death, heart failure, or a final LVEF <45% (6.7% vs. 24.4%, p = 0.02).

CONCLUSIONS: Combined treatment with enalapril and carvedilol may prevent LVSD in patients with malignant hemopathies treated with intensive chemotherapy. The clinical relevance of this strategy should be confirmed in larger studies. (Prevention of Left Ventricular Dysfunction During Chemotherapy [OVERCOME]; NCT01110824)

- After three cycles patient has CHF NYHA IV
- She was hospitalized
- **Her echo showed:**
  - Dilated LV cavity
  - Severe impairment of contractility EF 21%
  - Grade III DD
  - dilated impaired RV (TAPSE= 0.7)
  - mild MR
  - moderate TR and PASP of 45 mmHg

Are these changes reversible or not?

A. Yes

B. No

Are these changes reversible or not?

A. Yes

B. No

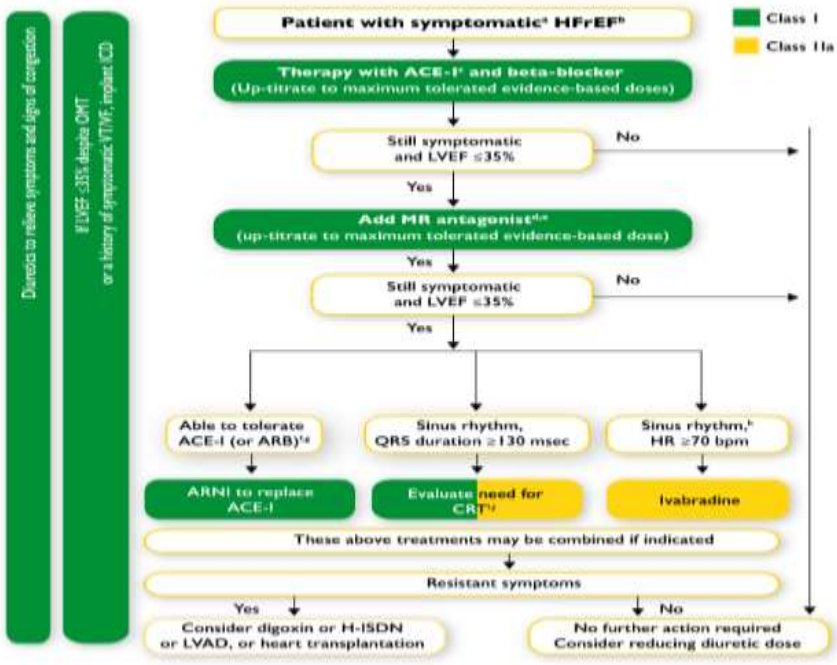
LV Dysfunction / Heart Failure (Incidence %)

		Myoc. Dysfunction	Heart Failure
Chemotherapeutics	**Anthracyclines** (Doxorubicin, Epirubicin, etc.)		1-48% (dose dependent)
	Alkylating agents (Cyclophosphamide, etc.)		7-28 % (dose dependent)
	Antimicrotubule agents (Doxotaxel, Paclitaxel)	1-13%	
Targeted agents / Biologicals	**Anti-HER2** (Trastuzumab, Lapatinib, Pertuzumab)	3-18 %	0-4 %
	Anti-VEGF (Bevacizumab, Sunitinib, Sorafenib, Pazopanib etc.)	3- 15 %	1-10%
	BCR-ABL inhibitors (Imatinib, Dasatinib, Nilotinib)	1- 4 %	
	Proteasome inhibitors (Bortezomib, Carfilzomib)	2-25%	

So what's the plan now?

3.1.5 Patients with heart failure during and following cancer treatment

Cancer patients presenting with clinical HF during or following cancer treatment should be treated according to current ESC guidelines for HF.[176,251] When presenting during chemotherapy, referral to a cardio-oncology specialist service is preferable, and close liaison with the oncology team is required to determine the necessity and duration of any interruption of cancer treatment,



Do we need a long term survaillence program?

A. Yes

B. No

Do we need a long term surveillance program?

A. Yes

B. No

Indication of Long term surveillance

- Development of cardiotoxicity during treatment
- Initiation of cardio protective medication
- high cumulative anthracycline doses and/or chest radiotherapy (lifelong surveillance)
- survivors of childhood cancers.
- Elderly patients and in patients with risk factors for cardiotoxicity who have been treated with anthracyclines.

Key points

- Cancer patients treated with potentially cardiotoxic therapy are at high risk of developing HF
- Initial risk stratification is very important to reduce incidence of cardiotoxicity
- Many Diagnostic tools and biomarkers are available to estimate ventricular functions
- Tools selection changes according to patient condition

Key points

- Surveillance programs are tailored according to the type of chemotherapy and patient risk
- Preventive methods can reduce risk of cardiotoxicity
- Treatment of cardiotoxicity must be started at once
- Long term surveillance is needed to high risk patients, patients suffered from cardiotoxicity and extreme of ages

Thank you