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CONGESTIVE HEART FAILURE (J LINDENFELD, SECTION EDITOR)

Cardiac Toxicity of Anticancer Agents

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Abstract Modern cancer therapies are highly effective in the treatment of various malignancies, but their use is limited by the potential for cardiotoxicity. The most frequent and typical clinical manifestation of cardiotoxicity is left ventricular dysfunction, induced not only by cytotoxic conventional cancer therapy like anthracyclines, but also by new antitumor targeted therapy such as trastuzumab. The current standard for monitoring cardiac function, based on periodic assessment of left ventricular ejection fraction detects cardiotoxicity only when a functional impairment has already occurred, precluding any chance of preventing its development. A novel approach, based on the use of cardiac biomarkers has emerged in the last decade, resulting in a cost-effective diagnostic tool for early, real-time identification, assessment and monitoring of cardiotoxicity. In particular, prophylactic treatment with enalapril in patients with an early increase in troponin after chemotherapy has been shown to be very effective in preventing left ventricular dysfunction and associated cardiac events. In patients developing cancer treatment induced-cardiomyopathy, complete left ventricular ejection fraction recovery and a reduction of cardiac events may be achieved only when left ventricular dysfunction is detected early after the end of cancer treatment and treatment with angiotensin-converting enzyme inhibitors, possibly in combination with beta-blockers, is promptly initiated.

Keywords Cardiotoxicity · Cardiac toxicity · Cancer therapy · Left ventricular dysfunction · Angiotensin-converting enzyme inhibitors · Beta-blockers · Prevention · Treatment · Biomarkers · Troponin · Anthracycline · Trastuzumab · Anticancer agents

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Introduction

Advances in pharmacological cancer treatments (CT) have led in recent years to a significant improvement in the prognosis of oncologic patients, reducing mortality for many forms of cancer. However, to achieve this result a considerable price has been paid in terms of cardiac side effects associated with the intensive anti-cancer treatment. Not only traditional cytotoxic chemotherapeutic agents, such as anthracycline (AC), but also novel, so called "targeted", therapies, such as monoclonal antibodies and small molecule tyrosine-kinase inhibitors, may affect the heart, decreasing both quality of life and survival of patients (Table 1) [1••, 2]. The spectrum of cardiac side-effects of CT may include cardiac dysfunction leading to heart failure (HF), myocardial ischemia, arrhythmias, hypertension, myocarditis, pericarditis, and thromboembolism [1••]. Cardiac events associated with CT vary in incidence and may occur acutely (during or shortly after treatment), sub-acutely (within days or weeks after completion of CT), or chronically (weeks to months after CT). They also may occur as a late sequelae, many years after the end of treatment [1••].

The most frequent and feared clinical manifestation of cardiotoxicity is the development of left ventricular dysfunction (LVD), occurring mainly after AC-containing CT or trastuzumab, a monoclonal antibody targeting human epidermal growth factor receptor-2 (ErbB2, also called EGFR2 or HER2), over expressed in 20 %–25 % of breast cancers.

At present, preventing, monitoring, and treating cardiac side effects of CT represent a major challenge that both oncologists and cardiologists must face, to maximize the benefits in terms of oncologic prognosis while reducing cardiac risk.

AC-Induced Cardiotoxicity

Anthracycline-induced cardiotoxicity has been classified as "type 1." It is dose related, mainly caused by oxidative

Table 1 Systemic cancer drugs with important cardiovascular (CV) side effects and selected indications

Class/drug	Selected indications	Important CV side effects
Cytostatic chemotherapeutics		
Anthracyclines/analogues		
Doxorubicin	Lymphoma	Cardiac dysfunction/heart failure
Daunorubicin	Leukemia	
Epirubicin	Breast cancer	
	Ovarian cancer	
	Sarcoma	
Mitoxantrone	Leukemia	
	Multiple sclerosis	
Pyrimidine analogues		
Fluorouracil (5-FU)	Colorectal cancer	Coronary spasms/ischemia
Capecitabine	Breast cancer	
Alkylating agents		
Cyclophosphamide	Breast cancer	Myocarditis (rare)
Cisplatin	Genitourinary cancer	Thrombosis
Antimicrotubule agents		
Paclitaxel	Breast cancer	Bradycardia
	Colorectal cancer	
Signaling inhibitors		
Anti-HER2		
Trastuzumab	Breast cancer	Cardiac dysfunction
Lapatinib	Gastric cancer	
Angiogenesis inhibitors/anti-VEGF		
Bevacizumab	Gastrointestinal cancer	Hypertension, endovascular damage
Sunitinib	Renal cell carcinoma	
Sorafenib	Hepatocellular carcinoma	
BCR-ABL inhibitors		
Imatinib	Leukemia	Edema, cardiac dysfunction (rare)
Dasatinib	Gastric cancer	QTc prolongation
Nilotinib		

Modified with permission from: Suter TM, Ewer MS. Cancer drugs and the heart: importance and management. Eur Heart J. 2012. [Epub ahead of print] [2]

VEGF vascular endothelial growth factor

mechanisms, leading to apoptosis and necrosis, and it tends to be progressive and irreversible [3].

Several risk factors predisposing patients to AC-induced cardiotoxicity have been identified. Among them, the strongest predictor for cardiac damage is the cumulative dose of AC administered. Other factors include concurrent administration of other cardiotoxic agents, prior AC treatment, history of cardiovascular disorders, older and younger age, female gender, pre-existing cardiac disorder, and prior mediastinal irradiation [4–6].

The suggested main mechanism of AC-induced damage is via generation of reactive oxygen species (ROS) by iron-AC complexes, leading to lipid peroxidation and membrane damage [7, 8]. However, recently it has been suggested that the ROS model is not sufficient to entirely explain AC cardiotoxicity [7]. In fact there is strong evidence that AC cardiotoxicity arises from ROS-independent mechanisms, such as cardiomyocyte apoptosis or necrosis, disruption of normal sarcomere structure, and altered energetics impairing the cardiac cell ability to generate adequate contraction [9–12].

In particular, a considerable body of evidence points to mitochondria as the key targets for AC cardiotoxicity. In fact, in response to AC treatment, activation of several protein kinases, neuregulin/ErbB2 signaling, and transcriptional factors can modify mitochondrial functions that determine cell death or survival, through the modulation of the mitochondrial membrane permeability transition pore (mPTP). Indeed mPTP opening is associated with the release of cytochrome c from mitochondria into cytoplasm and cell death, so the inhibition of mPTP seems to be a valuable tool to prevent doxorubicin-induced cardiotoxicity [13].

In a recent review Stěrba et al. [14] observe that the interpretation of many findings in this field is complicated by the enormous heterogeneity of experimental models and frequent employment of acute high-dose treatments with little effort on confirmation of proposed hypotheses using long-term chronic

animal models. Hence, further investigation is warranted, including the search for alternative or complementary strategies of cardioprotective action beyond simple iron chelation [14].

Trastuzumab-Induced Cardiotoxicity

Trastuzumab may cause a different kind of LVD from AC, named "type 2" [3]. This form of cardiotoxicity is not dose-dependent, not associated with severe ultrastructural changes on myocardial biopsy and in most cases reversible after drug withdrawal [1••, 3]. However, "type 1 and type 2" classification has limitations, as trastuzumab may trigger irreversible cardiac damage in patients with severe preexisting cardiac disease, or potentiate AC "type 1" cardiotoxicity [2].

In fact, adjuvant treatment with AC and trastuzumab is associated with positive clinical outcomes in women diagnosed with breast cancer [15–18], but the concurrent and sequential use of these agents increases the risk for the development of LVD. Due to the unacceptable rates of associated cardiotoxicity, concurrent administration of AC and trastuzumab is contraindicated, despite its clinical efficacy [19], and all large adjuvant trials have evaluated only the sequential strategy of trastuzumab and AC administration. Even with sequential therapy, however, LVD remains an important clinical issue. Data from clinical trials indicate that AC use is associated with an approximate 2 % increase in asymptomatic or symptomatic LVD incidence [20–24], and AC followed by trastuzumab is associated with an approximate 4 % increase [25–29]. A recent retrospective cohort study of 12,500 women with invasive breast cancer evaluated the risk for HF and/or cardiomyopathy (CMP) associated with the "real-world" adjuvant AC and trastuzumab use [30•]. The study showed that AC and trastuzumab were primarily used in younger, healthier women and associated with increased HF/CMP risk compared with no chemotherapy for the first 5 years of follow-up. In particular, compared with women who received no chemotherapy, the hazard ratios suggest a 4-fold increase in the risk of HF/CM among women who received trastuzumab alone and a 7-fold increase in the risk of HF/CM for those who received AC plus trastuzumab [30•]. Although it has some important limitations, being an observational community-based study relying completely on the use of administrative data [for example accurate data on left ventricular ejection fraction (LVEF) testing and results are lacking], this is the first study to examine associations between AC and/or trastuzumab treatment and LVD in breast cancer patients outside of clinical trials [30•].

The pathogenesis of trastuzumab cardiotoxicity seems to be related to blocking ErbB2-receptor signal in myocytes, with subsequent impairment of important cell-protective, growth-promoting, anti-apoptotic pathways in the myocardium [31–34]. Studies have demonstrated that activation of the ErbB2 signaling by neuregulin-1 (NRG), a member of the EGF-like growth factors family, improves cardiomyocyte function and survival in the heart [35]. In fact ErbB2 function seems to be required for the repair of oxidative damage caused by AC and its inactivation increases heart vulnerability to these compounds [3, 31, 34, 36]. Hence, up-regulation of the cardiac neuregulin/ErbB2 pathway may be one strategy to limit myocardial AC injury [13].

It's worth noting that all the studies that are underway to clarify the pathogenesis of cardiac damage induced by novel antineoplastic drugs such as trastuzumab are important to develop strategies aimed at the prevention of cardiotoxicity. In addition, they might also provide novel insights into the pathogenesis of non-cancer therapy-induced human heart disease [37].

Diagnosis of Cardiotoxicity

CT-induced LVD is often subclinical until a certain threshold of myocardial injury is exceeded. Therefore the sensitivity of symptoms and signs of HF for early diagnosis of cardiotoxicity is very limited. Several methods for early detection of subclinical cardiotoxicity have been proposed, but none of these diagnostic tools represent, at present, the gold standard.

Cardiac Imaging

Left Ventricular Ejection Fraction Monitoring

At present, the approach recommended by oncologic and cardiologic guidelines to detect CT-induced cardiac damage primarily relies on regular cardiac function monitoring, at baseline and during CT, by mean of LVEF measurement, using 2-dimensional transthoracic echocardiography (2D-TTE) and multi-gated radionuclide angiography [38–40].

The main limitation of this approach is its low sensitivity for detecting cardiotoxicity at an early stage, because no considerable change in LVEF occurs until a critical amount of myocardial damage has taken place. In fact, cardiac damage is usually detected only after functional impairment has already occurred, precluding any chance of preventing its development [41–43]. Furthermore, conventional 2D-TTE has low reproducibility in comparison with radionuclide imaging tests in patients receiving AC, and is limited by foreshortening errors, reliance on geometric assumptions, dependency on acoustic windows, and variable operator skill [44].

Improving Acquisition and Measurement of LVEF

Contrast-enhanced echocardiography has shown to improve the endocardial border definition and the identification of the true apex of the heart, allowing for accurate and reproducible

assessments of LVEF [45–48]. Three-dimensional (3D) TTE allows a more accurate assessment of LV volume and LVEF, with good correlation with computed tomography and cardiac magnetic resonance imaging (CMR) and offers higher reproducibility and lower inter-observer variability [49–53]. In a breast cancer population of 50 females receiving adjuvant trastuzumab after doxorubicin, serial 3D-TTE assessment of LV end-diastolic volumes (EDV) has been shown to strongly correlate with CMR and/or MUGA-derived measurements of LVEDV. Hence, the authors propose 3D-TTE as a feasible, accurate, and reproducible alternate imaging modality for the serial monitoring of LVEF in this setting [44].

Diastole Evaluation

In chemotherapy-induced cardiotoxicity, LVD may be preceded by alterations in diastolic function [54, 55]. Therefore, the evaluation of Doppler-derived diastolic indexes could represent an early sign of LVD. However, serial echocardiographic assessment of diastolic parameters failed to predict cardiotoxicity among 43 patients receiving AC and trastuzumab as the treatment of breast cancer [56]. Hence larger and prospective studies are needed to confirm the value of serial quantification of diastolic function in detecting early cardiotoxicity.

Strain and Strain Rate

Several works indicate that strain and strain rate imaging, obtained either with tissue Doppler measurements, or with the recently developed 2-D technique based on speckle tracking, is capable of detecting sub-clinical LVD in cancer patients. In a study of 56 asymptomatic pediatric patients 5 years post-AC treatment, significant reductions in regional Doppler-derived strain and strain rate measurements were observed while LVEF remained normal [57]. Reductions in myocardial function as measured by Doppler and 2D derived strain rate, were observed in 35 breast cancer patients following treatment with trastuzumab while LVEF measurements remained unchanged, with the 2D technique proving more sensitive to acute changes [58]. In a study of the efficacy of modified AC with 16 participants, significant reductions were observed in strain and strain rate after 6 cycles of PEGylated anthracycline, with no significant change in LVEF [59]. A prospective work from Fallah-Rad in patients receiving trastuzumab in the adjuvant setting showed that a decrease in global longitudinal and radial strain was able to detect pre-clinical changes in LV systolic function, before conventional changes in LVEF [60]. In a very recent publication, among 81 women treated with AC, followed by taxanes and trastuzumab, abnormalities of peak systolic longitudinal myocardial strain measured after completion of AC therapy predicted subsequent cardiotoxicity [61].

It is likely that strain and strain rate imaging will improve detection of subclinical myocardial damage, providing a more sensitive measure of the effects of cardiotoxic agents, but the value of these new techniques in clinical practice need further evaluation. In particular there is still no strain or strain rate value that provides a cut-off beyond which clinically manifest symptoms are more likely to occur and abnormal values may be difficult to define, especially in the setting of multiple coexisting risk factors [62] such as obesity, valvular disease, infiltrative disease, LV hypertrophy, myocardial infarction, as well as age and gender [63–71]. Other limitations of echocardiographic strain are its dependence on adequate acoustic windows to track endocardial borders for high fidelity measurements and the need for off-line analysis by expert echocardiographers [63].

Cardiac Magnetic Resonance

CMR is now considered the gold standard for measuring LVEF and subclinical alterations in cardiac structure and function [72–74] and might be used for the noninvasive assessment of LV volumes and LVEF in cancer setting [44, 75]. Evidence of subepicardial linear late gadolinium enhancement, similar to myocarditis pattern, was observed in the lateral portion of the left ventricles in 10 breast cancer patients treated with an AC and trastuzumab [75]. All these patients, with focal myocardial delayed enhancement, had already developed LVD, therefore the role of this marker in predicting LVD requires further investigation.

In a recent work by Armstrong et al. [76] CMR identified a high prevalence of CMP among adult survivors previously undiagnosed with cardiac disease, while 2D echocardiography demonstrated limited screening performance. The authors suggest that in high risk populations of patients previously exposed to cardiotoxic therapy, survivors with an LVEF 50 % to 59 % by 2D echocardiography should be considered for comprehensive cardiac assessment, which may include CMR [76]. Notably, CMR use in clinical practice is limited by cost, as well as by time required for acquisition and post-processing. However, CMR may be employed in selected patients with manifest LVD following exposure to chemotherapy, to evaluate alternative disease processes such as ischemic heart disease and infiltrative disorders [77].

Cardiac Biomarkers

During the last decade, a new approach, based on the use of cardiac biomarkers, in particular troponins, has emerged as a possible tool for the early identification, assessment and monitoring of CT-induced cardiotoxicity. This approach is minimally invasive and less expensive than echocardiography or the nuclear techniques, can be easily repeated without irradiation of the patients, and avoids the possibility of inter-observer variability.

Cardiac Troponins

Cardiac troponins - cardiac troponin T (TnT) and cardiac troponin I (TnI) - are at present considered the most tissue-specific biomarkers related to cardiac damage [78]. As well as being specific and sensitive markers of myocardial injury and widely used for the diagnosis and the risk stratification of acute coronary syndromes [79], their use has been extended to detect cardiac damage in other clinical settings, such as LV hypertrophy, HF, acute pulmonary embolism, blunt trauma, sepsis, stroke, renal insufficiency, sepsis, and cardiotoxicity associated with CT drugs [78, 80–83].

The utility of monitoring serum troponin to detect AC-induced cardiotoxicity was first reported in studies on animal models, where the amount of marker increase in the serum correlated both with the cumulative dose of AC administered and the degree of late cardiac impairment [84, 85].

Similarly, in a population of children treated with doxorubicin for acute lymphoblastic leukemia, Lipshultz et al. [86] showed that TnT increased in about 30 % of cases and the magnitude of TnT elevation predicted LV dilatation and wall thickening. In a subsequent larger randomized study, the same authors selected TnT as a biomarker for monitoring the effect of dexrazoxane as a cardioprotective agent in 206 pediatric patients with acute lymphocytic leukemia: dexrazoxane was associated with less frequent TnT elevations compared with a placebo, but the relationship between TnT increase and changes in cardiac function was not determined [87]. More recently, in the same population, followed-up for 5 years after treatment, the authors reported that children with at least 1 increase in TnT during CT showed significant late cardiac abnormalities at echocardiography [88, 89].

Studies from our group have shown that TnI is also a sensitive and specific marker for myocardial injury in adults treated with high-dose CT, and is also able to predict, at a very early phase, both development and severity of future LVD [90–93]. In the largest of these studies [93], we measured TnI soon after high-dose chemotherapy (early TnI) and 1 month later (late TnI) in a population of 703 patients with various malignancies. Patients were grouped according to 3 different patterns of TnI release. Tn I was consistently within the normal range in 70 % of cases, increased at only early evaluation in 21 %, and increased at both early and late evaluations in 9 %. In patients without TnI elevation no significant reduction in LVEF was observed during the 3.5-year-follow-up, and there was a very low incidence of cardiac events (1 %) . In contrast, a greater incidence of cardiac events occurred in TnI-positive patients. In particular, the persistence of the TnI elevation 1 month after CT was consistent with greater cardiac impairment and a higher incidence of events, in comparison with patients showing only a transient increase in the marker (84 % vs 37 %; $P<0.001$). Thanks to its high negative predictive value (99 %), TnI allows us to identify low-risk patients who will not require further cardiac monitoring. In contrast, TnI-positive patients require more stringent surveillance, particularly those showing a persistent TnI increase.

Other authors have shown that serial troponin measurements are useful for the early detection of cardiotoxicity even after minor AC exposure [94–96]. Auner et al. [94] reported a TnT increase in 15 % of patients treated with standard doses of AC, with a peak level at around 18 days after therapy. Patients with an elevated TnT level showed a significantly greater absolute decrease in LVEF than those without an elevation in the marker (10 % vs 2 %; $P=0.017$). Specchia et al. [95] described a significant LVEF reduction in TnI positive patients treated with AC for leukemia. Kilickap et al. [96] observed increased TnT levels in 34 % of patients in the first 3–5 days following administration of standard doses of AC; again, this increase was predictive of LVD. More recent studies have evaluated a possible role of troponins in the early detection of cardiac injury in patients undergoing treatment with newer targeted CT. In 251 breast cancer patients treated with trastuzumab [97] TnI was able to accurately identify patients at risk of developing LVD and, among them, those who were less likely to recover from cardiotoxicity, despite optimized HF treatment. In fact, LVD occurred in 62 % of patients showing an increase of TnI during trastuzumab treatment, and in only 5 % of those with normal TnI value ($P<0.001$). Patients showing an increase of TnI during trastuzumab treatment had a 3-fold decrease in the chance of recovery from LVD, and had a higher incidence of cardiac events. Indeed, elevated troponin after trastuzumab is a marker for worse prognosis, allowing us to distinguish patients with a more favorable cardiac outcome from those in whom close cardiologic monitoring is mandatory and for whom prophylactic strategies for prevention of clinical and subclinical cardiotoxicity should be planned [98].

In a prospective study, Schmidinger et al. [99] reported an increase in TnT in 10 % of patients with metastatic renal cancer treated with tyrosine-kinase inhibitor sunitinib or sorafenib. Ninety percent of them showed a decrease in LVEF or regional contraction abnormalities following the increase in TnT. Morris et al. [100] showed increased TnI in patients receiving both trastuzumab and lapatinib — a tyrosine-kinase inhibitor — following AC-based CT. The timing of detectable TnI preceded maximum decline in LVEF. These data suggest that troponins may be useful for assessing cardiotoxicity in patients treated with both conventional and newer anti-cancer therapies. Apparently, the release of troponin reflects a final common event for multiple cardiotoxic mechanisms.

In a very recent multi-center study Sawaya et al. [61] have explored a possible employment of high-sensitivity (HS) troponins in this setting. The authors employed HS-troponins and echocardiographic parameters of myocardial deformation to detect LVD in patients receiving AC, taxanes, and trastuzumab. They evaluated global and regional myocardial

function by tissue Doppler and strain rate imaging, combined with HS-TnI, at baseline, 3, 6, 9, 12, and 15 months during CT. Decreases in peak longitudinal strain and increases in HS-TnI concentrations, at the completion of the AC treatment, were predictive of subsequent LVD. On the other hand, changes in LVEF, diastolic function, and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), evaluated at the same time points, were not predictive of later LVD. As an elevation in TnI or a decrease in longitudinal strain was associated with higher sensitivity and specificity compared with each parameter alone, this study suggests that combining biomarkers with the newest echocardiographic techniques may have a greater value in the prediction of cardiotoxicity [61].

Prevention of Cardiotoxicity

Before starting a potentially cardiotoxic CT, a careful cardiological evaluation including standard 12-lead ECG and assessment of LVEF, preferably by ultrasound, is mandatory [101]. Since assessment of baseline cardiological status may influence the choice of CT regimen, the need for a multidisciplinary consultation (oncologist/cardiologist) should always be considered before treatment [102, 103].

Several preventive measures have been proposed to reduce the risk of cardiotoxicity, including limiting cumulative CT dose, altering AC administration, using less cardiotoxic AC analogues, adding cardioprotectants to the regimen, and the detection of early signs of cardiotoxicity by biomarkers [103–109].

Carvedilol, a beta-blocker with alpha-1-blocking vasodilatory properties, has also showed strong antioxidant activity that lends it a cardioprotective effect against doxorubicin [103]. This favorable effect was confirmed in an in vitro study [106], and in a randomized study in which prophylactic use of carvedilol prevented LVD and reduced mortality in a small population of patients treated with AC [107]. The protective effect of nebivolol against AC-induced CMP has been demonstrated in a very recent randomized study. In 27 patients receiving nebivolol during AC-therapy LVEF and NT-proBNP remained unchanged after 6 months from baseline; conversely, in the placebo group a significantly lower LVEF and a higher NT-proBNP value were observed [110].

Although most of these strategies are promising, each has some limitations, such as the possible compromise of CT clinical success, high costs, and poor positive predictive value. The most critical limitation however is that all of the above mentioned strategies address all cancer patients undergoing CT, with a very high cost-benefit ratio. The possibility of identifying patients at higher risk of developing cardiotoxicity by cardiac biomarkers, in particular by troponins, provides a rational alternative directed at counteracting the ongoing myocardial damage and preventing the development of LVD and adverse cardiac events. The usefulness of TnI in selecting patients for prophylactic cardioprotective therapy was investigated in a randomized, controlled trial, carried out at our institute [111]. The cardioprotective effects of enalapril were evaluated in 413 patients treated with high-dose AC. The 114 (24 %) patients showing early TnI increase were randomized either to receive enalapril (ACEI group, n=56) or not (controls, n=58). Treatment was started 1 month after CT and was continued for 1 year. The maximal tolerated dose of enalapril in the ACEI group was 16±6 mg/d. In the ACEI group, LVEF did not change during the follow-up period, whereas, in patients not receiving enalapril, a progressive reduction in LVEF and an increase in end-diastolic and end-systolic volumes were observed (Table 2). Moreover, in the ACEI group a

Table 2 Echocardiographic parameters during the study period

		Baseline	Rand.	3 months	6 months	12 months	*P* value*
EDV (mL)	ACEI-group	101.7±27.4	100.2±26.1	98.1±27.8	97.5±24.5	101.1±26.4	0.045
	Controls	103.2±20.1	103.9±21.0	106.4±21.0	107.1±23.9	104.2±25.6	
ESV (mL)	ACEI-group	38.6±10.8	38.7±10.4	37.3±10.9	37.4±10.3	38.5±11.2	<0.001
	Controls	38.8±10.2	40.5±12.2	49.8±17.6	51.8±16.9	54.4±20.1 †	
LVEF (%)	ACEI-group	61.9±2.9	61.1±3.2	61.9±3.3	61.6±3.9	62.4±3.5	<0.001
	Controls	62.8±3.4	61.8±4.3	54.2±8.1	51.9±7.9	48.3±9.3 †	

*P value for repeated measures analysis of variance. † = P<0.001 vs baseline.

EDV end-diastolic volume, *ESV* end-systolic volume, *LVEF* left ventricular ejection fraction, *Rand.* randomization.

Modified from Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006;114:2474–81. [111]

lower incidence of adverse cardiac events was observed than in untreated patients (2 % vs 52 %; $P<0.001$) [111].

Treatment of CT-Induced Left Ventricular Dysfunction

There are no well established recommendations for treatment of cancer patients who develop HF after anticancer treatment. Even if the use of angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers (BB), as recommended by cardiologic international guidelines [112], may be highly effective also in this setting, current management focuses mainly only on treatment of symptomatic patients and often the tendency is not to treat these patients aggressively [113]. In fact, cancer patients with CT-induced CMP have systematically been excluded from large randomized trials evaluating the efficacy of modern HF therapy. Furthermore, the use of ACEI and BB in the particular setting of patients with AC-induced LVD has never been fully investigated. As a consequence, there is some concern whether the use of these classes of drugs can be transferred directly to this particular clinical setting with similar long-term benefits, particularly in patients with asymptomatic LVD.

A recent prospective study [114] showed that time elapsed from the end of CT to the start of HF treatment with ACEI and, when tolerated, with BB, is a crucial variable for recovery of LVD. The likelihood of obtaining complete LVEF recovery is higher in patients in whom HF treatment is initiated within 2 months from the end of CT. After this time limit, however, the percentage of full recoveries progressively decreases and no complete LVEF recovery is observed after 6 months. It must be stressed that, in this study, the clinical benefit was more evident in asymptomatic patients, emphasizing the crucial importance of an early detection of cardiotoxicity and suggests that an aggressive approach, based on the association of both ACEI and BB, should always be considered, and attempted, in all cases of AC-induced CMP.

Cardiac progenitor cells (CPCs) may play a role in the treatment of AC-induced cardiotoxicity. In preclinical studies, rats, which had developed AC-induced LVD have improved survival and LV function when treated with intramyocardial injections of immunocompatible CPCs [115]. De Angelis et al. [116•] demonstrated that rats that developed AC-induced cardiotoxicity, after 3 weeks of doxorubicin treatment, and were subsequently treated with CPCs, had a 66 % decrease in mortality at 6 weeks, compared with control rats treated with only the vehicle; LV function also improved. These data suggest that CPCs may be considered as a potential translational therapy in the future, helping to promote cardiac repair after AC-induced cardiotoxicity. These results raise the possibility that autologous CPCs can be obtained before antineoplastic drugs are given to cancer patients and subsequently administered to individuals who are particularly sensitive to the cardiotoxicity of these agents for prevention or management of HF [115, 116•].

Trastuzumab-related cardiotoxicity seems to have a more favorable outcome, as cardiac function in most cases improves after withdrawal of the drug. Moreover, in many cases, after LVD recovery by a therapy with ACEI and BB, a re-challenge with trastuzumab does not necessarily lead to redevelopment of LVD or HF [117, 118]. However, the concept that trastuzumab-related LVD is reversible is under discussion [36]. Follow-up data from the largest trials show that in many patients treated with AC and sequentially with trastuzumab, some decline from baseline often persists despite optimal HF therapy [119]. Moreover, because patients who developed LVD in the adjuvant trastuzumab trials

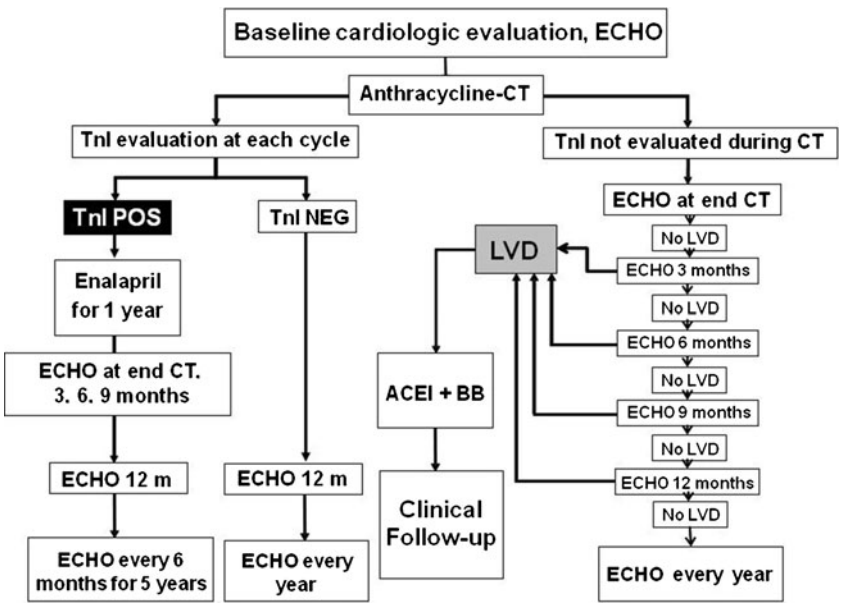

Fig. 1 Algorithm for the management of cardiotoxicity in patients receiving anthracyclines. *ACEI* angiotensin-converting enzyme inhibitors, *BB* beta-blocking agents, *CT* chemotherapy, *ECHO* echocardiogram, *TnI* Troponin I, *LVD* left ventricular dysfunction. (Modified with permission from Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al.; ESMO Guidelines Working Group. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2012;23(Suppl 7): vii155–66) [101]

were not treated in a systematic manner [36, 41, 118,], no evidence-based recommendations for its management have yet been formulated. The natural history of trastuzumab-induced cardiotoxicity is currently unknown, and because no prospective randomized trials have investigated this point, some uncertainties regarding early diagnosis and management of trastuzumab-induced LVD still exists.

Conclusions

Anticancer treatment-induced cardiotoxicity still remains a serious problem, strongly affecting both quality of life and overall survival of cancer patients. The most effective approach for minimizing cardiotoxicity is its early detection and prompts prophylactic treatment initiation. The current standard for monitoring cardiac function detects cardiotoxicity only when a functional impairment has already occurred, which doesn't allow any early preventive strategy. The role of TNI in identifying patients with subclinical cardiotoxicity and their treatment with ACEI, to prevent LVD and cardiac events, is emerging as an effective strategy against these complications. When this kind of approach is not feasible, a complete LVEF recovery and a reduction of cardiac events may be achieved if LVD is detected early after the end of chemotherapy and treatment with ACEI, possibly in combination with BB, is promptly initiated (Fig. 1).

Conflict of Interest Alessandro Colombo declares that he has no conflict of interest.

Carlo Cipolla declares that he has no conflict of interest.

Marta Beggiato declares that she has no conflict of interest.

Daniela Cardinale declares that she has no conflict of interest.

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- •• Of major importance

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