Early Detection of Cardiac Damage

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Introduction

Advances in the early diagnosis, staging, and therapy have significantly reduced the mortality and increased longevity in cancer patients. An estimated 14.5 million people are currently living with a history of cancer in the USA. This number is projected to rise to 19 million over the next 10 years [1]. A significant proportion of cancer survivors are living with long-term adverse effects of cancer therapy, involving multiple organ systems. Cardiovascular toxicity of cancer therapy is a major concern in this regard.

Cancer therapies, especially anthracyclines and monoclonal antibodies, have been linked with increased rates of cardiotoxicity (CTX). The clinical manifestations of cardiotoxicity are broad and can include heart failure, cardiomyopathies, arrhythmias, ischaemia, valves heart disease, pericardial disease, hypertension, or thrombosis. Cancer therapeutics-related cardiac dysfunction (CTRCD) is reported in 2–3% in randomized trials on breast cancer women treated with anthracyclines and trastuzumab but can reach up to 26% in observational studies [2].

It is clear that symptom-based monitoring is ineffective because when they occur, damage is already advanced, and therefore it is recommended after a baseline evaluation to monitor cardiac function to promptly detect any variation. Early detection and quantification of cardiac damage is required to readily intervene with cardioprotective therapy and to allow the prosecution of antineoplastic treatment and avoid the need of its discontinuation. Therefore, cardio-oncology is a newly emerging subspecialty of cardiology with the aim of monitoring, early diagnosis, prevention, and treatment of cardiotoxicity related to cancer therapies and careful planning of chemotherapy in patients with pre-existing cardiovascular disease to avoid overt cardiotoxicity and heart failure.

Many strategies are available to monitor cardiac function during or after chemotherapy including cardiac imaging (echocardiography, nuclear imaging, cardiac magnetic resonance) and biomarkers (troponin, natriuretic peptides).

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Table 16.1 Diagnostic tools for the detection of cardiotoxicity

Technique	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 CTX • GLS: >15% relative percentage reduction from baseline may suggest risk of CTX	• 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	• >10 percentage points decrease in patients with CTX	• Reproducibility	• Cumulative radiation exposure • Limited structural/ 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 borderline	• Accuracy, reproducibility • Detection of diffuse myocardial fibrosis using T1/T2 mapping	• Limited availability • Patient's adaptation (claustrophobia, breath hold, long acquisition times)
Cardiac biomarkers: – TnI – hsTnI – 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 further 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

Adapted from Zamorano et al. [3]
BNP B-type natriuretic peptide, *CTX* cardiotoxicity, *GLS* global longitudinal strain, *hsTnI* high-sensitivity troponin I, *LLN* lower limit of normality, *LVEF* left ventricular ejection fraction, *NT-proBNP* N-terminal fragment B-type natriuretic peptide, *TnI* troponin I

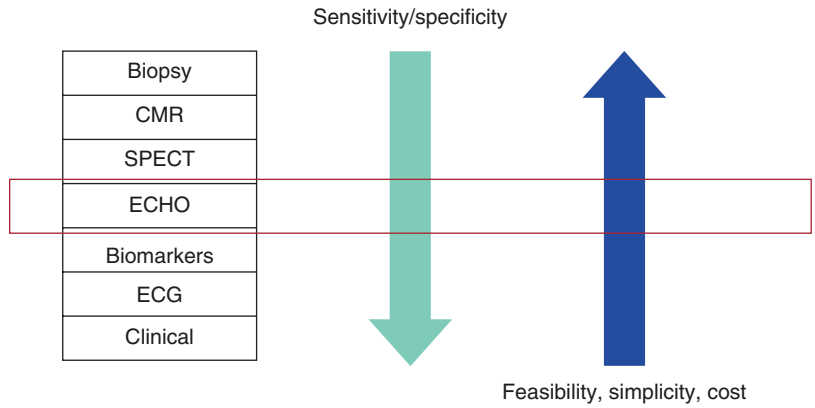

Fig. 16.1 Echocardiography vs. other modalities for detection of cancer therapeutics-related cardiac dysfunction. (Adapted from Zito et al. [4])

The choice of different modalities depends upon local expertise and availability [3]. Table 16.1 summarizes the main techniques available and current diagnostic criteria.

Echocardiography

Monitoring with 2D echocardiography is the most frequently used technique in clinical practice because of its safety, wide availability, repeatability, and low cost (Fig. 16.1). Echocardiographic technology has been continuously evolving, with two major developments being real-time three-dimensional echocardiography (3DE) and myocardial deformation imaging.

For conventional analysis, left ventricular volumes and left ventricular ejection fraction (LVEF) are the most widely used parameters to detect CTX [5, 6]. The method for 2D echocar-

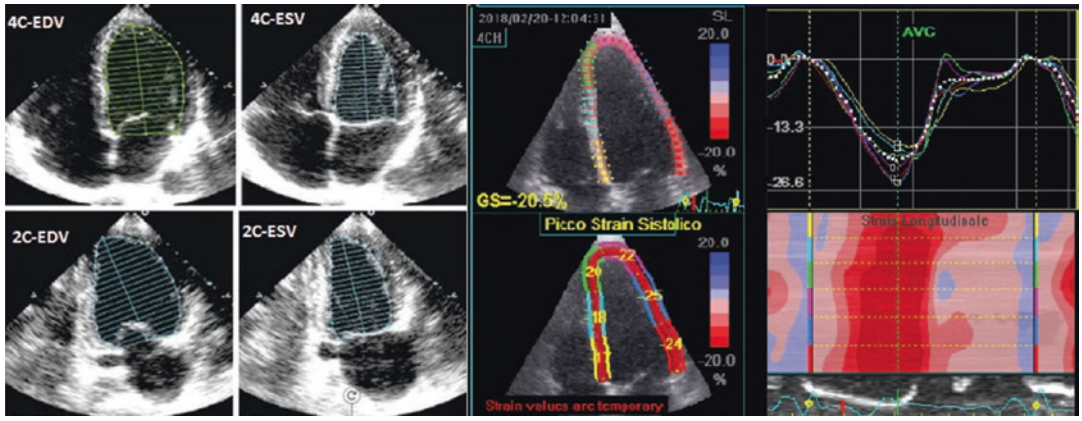

Fig. 16.2 Left panel: Simpson's biplane method. Right panel: speckle-tracking echocardiography (STE)

diographic volume calculations recommended by the European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) is the biplane method of disc summation (modified Simpson's rule). Volume measurements are based on tracings of the blood tissue interface in the apical four- and two-chamber views. At the mitral valve level, the contour is closed by connecting the two opposite sections of the mitral ring with a straight line. Left ventricle (LV) length is defined as the distance between the middle of this line and the most distant point of the LV contour (Fig. 16.2, left panel). The LVEF is then calculated using the following formula: LVEF = (LVEDV − LVESV)/LVEDV; (LVED LV end-diastolic volume, LVESV LV end-systolic volume). Normal LVEF using biplane method of discs is 63% ± 5%, and LVEF in the range of 53–73% is classified as normal [7].

CRTCD is defined as a 10% decrease of left ventricle ejection fraction to a value below the normal limit of normal confirmed in repeated studies (at 2–3 weeks).

Newer echocardiography techniques, using contrast echocardiography or 3D technology, have resulted in significant improvement in the accuracy of LVEF assessment. Contrast agents should be used to improve endocardial delineation when two or more contiguous left ventricle endocardial segments are poorly visualized in apical views [7, 8]. Contrast-enhanced images may provide larger volumes than unenhanced images that are closer to those obtained with cardiac magnetic resonance (CMR) [9].

In patients with good image quality, 3D echocardiographic measurements are accurate and reproducible and should therefore be used if available [7]. One of the advantages of 3D echocardiographic volume measurements is that they do not rely on geometric assumptions.

A small study of 50 patients with breast cancer undergoing serial LVEF assessments demonstrated that 3D echocardiography was feasible and reproducible for assessing changes in LV volumes and LVEF compared with the gold standard cardiac MRI [10]. Thavendiranathan et al. showed that non-contrast 3D echocardiography was the most reproducible technique for LVEF assessment, capable of detecting smaller changes in LVEF (~5%) [11].

Unfortunately, impairment of LVEF is detectable only after that a considerable cell loss has taken place [12, 13] and thus too late to allow effective prevention. For this reason, new markers of systolic dysfunction have been investigated to earlier detect damage and predict cardiotoxicity. Deformation analysis seems to be a promising tool to detect myocardial dysfunction at an earlier stage [14].

Besides monitoring systolic function, it is recommend in cancer patients to perform a comprehensive echocardiographic evaluation measuring diastolic function and evaluating cardiac valves and pericardium [15].

Diastolic function is frequently impaired in cancer studies [4, 16]. Several studies demonstrated an early reduction in the e' velocity of the mitral annulus using tissue Doppler imaging (TDI), which remained reduced during and for several years after treatment [17, 18]. However, the use of the E/e' ratio remains questionable in the oncological setting because E and e' velocity fluctuations in these patients may be the consequence of changes in loading conditions associated with chemotherapy (e.g. nausea, vomiting, and diarrhoea) more than the result of a real change in left ventricle diastolic performance [4].

Chemotherapeutic agents do not directly affect cardiac valves, but valve heart disease may manifest in oncological patients for different reasons such as:

(a) Pre-existing valve disease
(b) Concomitant radiation therapy that causes calcification and fibrosis of the aortic root, aortic cusps, mitral valve annulus, tips, and commissures [19]
(c) Infective endocarditis favoured pancytopenia associated with chemotherapy
(d) Mitral regurgitation secondary to annular dilatation or apical tethering due to CRDT and tricuspid regurgitation as consequence of right ventricle dysfunction and pulmonary hypertension [3, 15].

Echocardiography is the assessment method of choice, and 3D echocardiography may be useful, particularly for the evaluation of mitral valve commissures. CMR and computed tomography (CT) may be used to assess the severity of the valve disease but usually are not required in routine clinical practice [15].

According to the current EACVI/ASE recommendations [15], patients with baseline or changing valve findings should undergo careful evaluation of valve structure and function during and after cancer treatment.

Pericardial disease is also common in oncologic patients, as consequence of cancer therapies or metastasis, and usually occurs as pericarditis and pericardial effusion and sometimes as constrictive pericarditis especially after radiotherapy or high-dose chemotherapy. Acute pericarditis may occur predominantly with the use of anthracyclines, cyclophosphamide, cytarabine, and bleomycin. Transthoracic echocardiography is the method of choice for the evaluation of patients with suspected pericardial disease due to chemotherapy, but CT can be helpful to identify calcification, and CMR should be considered in the evaluation of primary tumours of the heart. Pericardial effusion should be quantified and graded according to standard methods [20], and it is important to evaluate the presence of echocardiographic and Doppler signs of cardiac tamponade in this setting of patients.

Myocardial Deformation Imaging

LVEF reflects the volumetric variation of the ventricle during the cardiac cycle, which depends on the size and shape of the left ventricle, the contraction of the global myocardium, the integrity of the mitral and aortic valve, and the preload and post-load. In contrast, myocardial deformation analysis reflects the length variation of the myocardial fibres, and thus it is a measure of intrinsic contractility (Fig. 16.2, right panel) [14].

By the analysis of the motion of speckles in the two-dimensional ultrasonic image, this technique allows a non-Doppler angle-independent objective analysis of myocardial deformation, with the possibility to quantify longitudinal, circumferential, radial function and torsion. The best validated strain measure is global longitudinal strain (GLS). Speckle-tracking echocardiography (STE) has recently demonstrated to be an accurate, feasible, and reproducible measure of cardiac function [21].

The maximum extent of systolic myocardial deformation (i.e. peak systolic strain) and its

peak rate (i.e. peak systolic strain rate) were used regionally and globally [4]. One of the first studies using 2D-STE strain was performed in 2008 and demonstrated that this technique recognized early damage caused by anthracyclines [22].

Many authors subsequently focused their efforts on this topic to identify CTX in patients previously treated with oncologic therapies to predict CTX development.

2D-STE was more sensitive than LVEF reduction for the early recognition of asymptomatic left ventricle systolic dysfunction caused by chemotherapy in children and adults [4, 23–25].

Other studies [26, 27] provided information on serial evaluations of cardiac function before and after chemotherapy by comparing GLS with LVEF. They found that GLS was the most sensitive and specific measurement for the detection of subclinical myocardial injury early after anthracycline exposure (from 1 day to 3 months after the treatment in the different studies) because GLS decreased significantly without any reduction in LVEF.

A prospective study of 81 patients with breast cancer evaluated the use of longitudinal strain assessed at baseline, after completion of anthracycline-based therapy, and every 3 months during trastuzumab. A longitudinal strain value lower than −19% (less negative or a lower negative number) after the completion of anthracyclines was predictive of CTX [28]. The accuracy of the prediction increased when cardiac troponin was also measured [28]. Measuring the percentage variation of GLS between follow-up and baseline seems to be a specific approach to early detect CTX. Negishi K et al. demonstrated that an 11% reduction of GLS (95% confidence interval, 8.3–14.6%) was the optimal cut-off, with sensitivity of 65% and specificity of 94% for detecting CTX [29].

The European Society of Cardiology (ESC) recently provided a document [3] containing a practical approach for monitoring patients undergoing cancer therapy with GLS. Measurements of GLS during chemotherapy should ideally be compared with baseline value, and a relative percentage reduction of GLS of less than 15% from baseline is very likely to predict future CRTD (Table 12.1). The same vendor-specific ultrasound machine should be used when monitoring STE for longitudinal follow-up of patients with cancer.

A small study demonstrated that early therapeutic intervention with beta-blocker based on strain reduction alone allowed a normalization of strain values during follow-up; however evidences demonstrating a clinical impact of this approach are still lacking [30]. The multicentre, randomized SUCCOUR (Strain Surveillance During Chemotherapy for Improving Cardiovascular Outcomes) trial is designed to determine if a strain-based strategy for initiation of cardioprotective therapy is superior to one based on LVEF.

Three-dimensional speckle-tracking echocardiography (3D-STE) is a promising techniques in the evaluation of myocardial function. The possibility of evaluating the deformation on a full-volume model avoids the errors derived from the use of two-dimensional images [31].

Recent studies demonstrated that childhood cancer survivors evaluated by 3D-STE had significantly reduced GLS and torsion and greater systolic dyssynchrony index in comparison to healthy controls [32]. Mornoş et al. found that GLS evaluated by 3D-STE was superior to biomarkers and to LVEF in predicting future development of cardiotoxicity [33].

Although 3D-STE is a promising method, there are few studies on small populations that compared this technique to the other standard methods. Moreover, 3D-STE is not widely available in the echo-labs; thus its use has still to be considered reserved to research purpose.

Nuclear Imaging and Cardiac Magnetic Resonance

Radionuclide angiography (MUGA) was referred as the gold standard to evaluate left ventricle systolic function in patients undergoing chemotherapy for many years [34]. MUGA makes use of 99mTC-erythrocyte labelling enabling the visualization of the cardiac blood pool by γ-camera with electrocardiogram-triggered acquisitions.

The final result provides a highly reproducible and precise quantification of LV volumes and dyssynchrony independently of geometrical assumption [35]. The main disadvantage of MUGA is radiation exposure, which reduces its use given the increasing availability of other radiation-free imaging techniques (Table 12.1).

MUGA also provides limited structural and functional information on other cardiac structures (right ventricle, left and right atrium, valves, and pericardium). Therefore, it is frequently used as an adjunct and complementary technique to echocardiography.

The need of a reliable and accurate detection method for early CTX has encouraged the introduction of second-line advanced imaging modality into the evaluation of chemotherapy-treated patients, such as cardiac magnetic resonance (CMR) (Table 16.1). CMR is an ionizing radiation-free imaging method recently accepted as the gold standard for quantifying biventricular volumes, function, and mass [36, 37].

The standard CMR approach for quantifying biventricular function parameters uses contiguous short-axis slices covering the entire ventricles acquired from a cine steady-state free precession (SSFP) sequence (Fig. 16.3) [36]. In the evaluation of CTX, the incremental value of CMR is represented by its capability for providing information on tissue characterization, such as oedema, hyperaemia, fibrosis, and iron overload. It also serves to evaluate the pericardium, especially in patients with chest irradiation.

Neilan et al. [38] showed that myocardial scar by late gadolinium enhancement CMR is infrequent in patients with anthracycline cardiomyopathy despite a reduced ejection fraction, and indexed LV mass by CMR imaging is a predictor of adverse cardiovascular events.

A new CMR parameter was recently proposed, the LV global function index, that combines left ventricular stroke volume, end-systolic and end-diastolic volumes, and mass, and a value less than 37% has been shown to be associated with the occurrence of cardiovascular events [39]. However, no data are available on this promising index in monitoring CTX [36].

Myocardial deformation can be evaluated by tagging techniques and, more recently, by using phase-contrast imaging. In the technique most frequently used, the myocardium is tagged with a grid of magnetic saturation lines at end diastole, allowing the analysis of deformation by tracking the distortion of the grid during systole.

In a recent study [40], measures of left ventricular systolic performance (LVEF and mean mid-wall circumferential strain) deteriorated

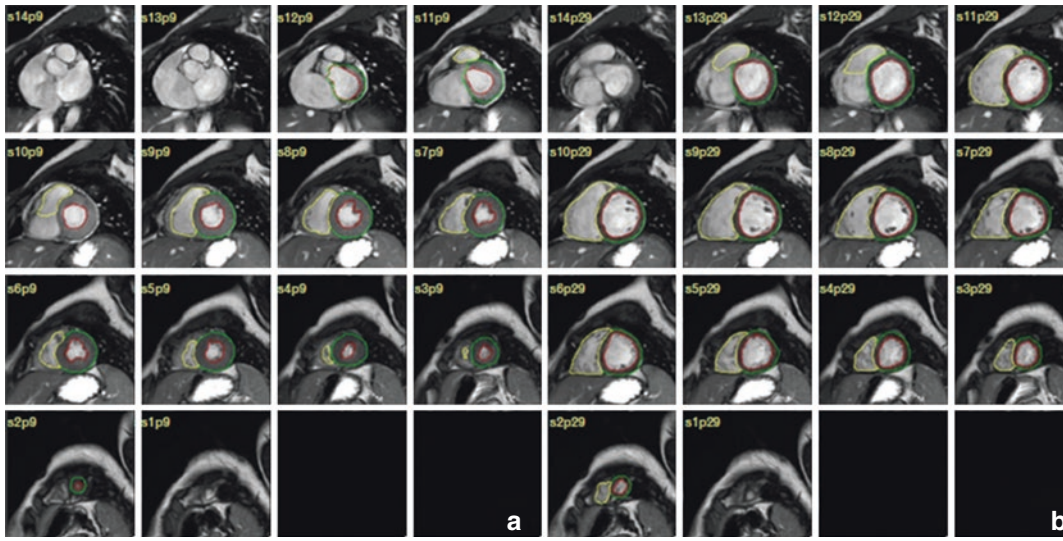

Fig. 16.3 Quantification of biventricular function by CMR. (**a**) End-systolic phases; (**b**) end-diastolic phases

early and remained abnormal 6 months after initiation of low to moderate doses of anthracycline-based chemotherapy. Authors did not appreciate new infarcts or fibrosis by late gadolinium enhancement.

Few studies evaluated the presence of oedema and fibrosis in patients treated with chemotherapy. Regarding the detection of myocardial oedema as early marker of cardiac damage, in this setting of patients, results are contrasting, and no prognostic data are available [41, 42].

The prevalence of non-ischaemic areas of LGE was reported between 6% and 100% [43, 44]. However, the role of the LGE in the prognostic stratification of these patients is not yet well defined [38, 44, 45].

LGE is able to detect only macroscopic fibrosis. However, oncologic patients can develop diffuse myocardial fibrosis that can be detected by T1 mapping with the evaluation of the extracellular volume (ECV). Small studies showed encouraging results on the use of T1 mapping in the detection of myocardial damage during and after chemotherapy [46–48].

Based on these evidences, T1 mapping seems to be a very useful technique in oncologic patients in order to detect changes in the molecular features of the myocardium prior to the occurrence of functional alterations. However, its prognostic role is still under investigation.

Cardiac damage induced by anthracyclines appears to be partially dependent on the alteration of intracellular iron metabolism. Unfortunately, evaluations of myocardial iron overload in patients treated with anticancer drugs have not yet been performed [36].

Actually, CMR is recommended for the quantification of LVEF when the quality of echocardiogram is suboptimal. In follow-up assessments, CMR is recommended for the quantification of LVEF in cases of possible discontinuation of chemotherapeutic regimens as a result of CTX or when LVEF estimation by echocardiography is controversial or unreliable due to technical constrains. Diastolic function by CMR is not usually recommended in current practice [15].

Biomarkers

The use of cardiac biomarkers during cardiotoxic chemotherapy may be considered in order to detect early cardiac injury. Currently, the most studied biomarkers for the early detection of cardiac damage induced by anticancer drugs are cardiac troponins (cTns) and natriuretic peptides (Table 16.1).

Cardiac troponins are sensitive and specific markers of myocardial injury and are widely used in cardiovascular medicine. Troponin I is a serum marker that detects damage of myofibrils and cardiomyocytes. It identifies acute injury due to ischaemia but also to other causes such as drugs.

Among troponins, TnI is the most widely studied serum biomarker of cardiotoxicity, its elevation can predict the future decline of myocardial function, and the amount of its elevation is correlated with patients' prognosis [49]. Particularly, it has been shown that in patients with cancer, treated with high doses of anthracyclines, the increase in cTn allows discrimination between patients with a low risk of developing chemotherapy-induced CTX and who do not need strict follow-up and those at high risk, which require a more rigorous cardiac monitoring [50].

In particular, patients with a persistent (early and late) increase in cTn show a greater reduction in LVEF at follow-up [51]. In patients treated with trastuzumab, the elevation of cTnI identified patients who developed CTX and who did not recover after interruption of treatment [52]. Less established is the role of troponin in predicting cardiotoxicity in patients treated with conventional doses of anthracyclines; in this setting high-sensitivity troponin (hsTn) is probably more useful (Table 16.2).

In patients with breast cancer, a recent study demonstrated that the combination of high-sensitivity troponin with GLS might provide the greatest sensitivity (93% when both are altered) and sensitivity (87%, when one of two parameters is altered) to predict future cardiotoxicity [28].

Main advantages of cTn use include wide availability, accuracy, reproducibility, and lower cost than imaging. Nevertheless, there are some uncertainties that still remain unre-

Table 16.2 Main studies evaluating the conventional and emerging biomarkers in the detection of cardiotoxicity (CTX)

Authors	Population	Results
Sawaya et al. [28]	82 patients with breast cancer treated with anthracyclines, taxanes, and trastuzumab who were evaluated every 3 months with echocardiography (strain) and blood sample (hsTnI, NT-proBNP, and ST2)	Myocardial strain and hsTnI, measured at the completion of anthracycline therapy, are useful in the prediction of subsequent cardiotoxicity
Ky et al. [53]	78 patients with breast cancer treated with doxorubicin and trastuzumab who were evaluated every 3 months for different biomarkers	Early increases in TnI and MPO levels offer additive information about the risk of cardiotoxicity in patients undergoing doxorubicin and trastuzumab therapy
Cardinale et al. [50]	251 patients with breast cancer treated with TZT with or without other chemotherapy (197 had prior exposure to anthracyclines)	TnI identifies patients at risk for developing cardiotoxicity and who are unlikely to recover following the completion of therapy
Cardinale et al. [51]	703 patients with various malignancies treated with high-dose chemotherapy. TnI measurement before chemotherapy at 1, 3, 6, and 12 months after the end of the treatment and every 6 months thereafter	Elevated TnI (cut-off >0.08 ng/mL) identified patients at greater risk of cardiac events (particularly the group with persistently elevated TnI)
Feola et al. [54]	52 patients with early breast cancer treated with anthracyclines	In patients who developed left ventricular systolic dysfunction, BNP but not TnI increase was observed
Suzuky et al. [55]	27 patients receiving anthracyclines are investigated by serial measurements of BNP, A-type natriuretic peptide, renin, aldosterone, angiotensin II, norepinephrine, epinephrine, and echocardiography	BNP levels are elevated after anthracycline administration. Patients with persistent elevations showed a poor prognosis
Sandri et al. [56]	NT-proBNP was measured after chemotherapy treatments in 52 patients affected by aggressive malignancies	Persistently increased NT-proBNP early after administration of HDC is strongly associated with development of cardiac dysfunction
Romano et al. [57]	71 patients who did not undergo high-dose chemotherapy with anthracyclines. NT-proBNP and cTnI level measurement before and 24 h after each cycle	NT-proBNP, but not troponin, showed abnormal values. LV impairment was significantly worse in patients with persistently elevated NT-proBNP levels
Lagoa et al. [58]	Measurements of the temporal evolution of selected biochemical markers after treatment of rats with doxorubicin (20 mg/kg body weight)	Quinone oxidoreductase-1 activity and increase of hydrogen peroxide production by NADPH oxidases are early biomarkers in doxorubicin cardiotoxicity
El Ghandour et al. [59]	In 40 NHL patients who received doxorubicin, human heart-type fatty acid-binding protein (H-FABP) was assessed 24 h after the first cycle of chemotherapy	H-FABP may serve as a reliable early marker for prediction of cardiomyopathy induced by doxorubicin
Horacek et al. [60]	53 patients undergoing HCT for various haematological malignancies	Increased release of GPBB could be considered a sign of acute subclinical CTX
Horie et al. [61]	Evaluate the role of miRNAs in acute Dox-induced cardiotoxicity in mice	When miR-146a "decoy" genes were introduced into cardiomyocytes, ErbB4 expression was up-regulated, and Dox-induced cell death was reduced

GPBB glycogen phosphorylase isoenzyme BB, *HCT* haematopoietic cell transplantation, *HDC* high-dose chemotherapy, *hsTnI* high-sensitivity troponin I, *LV* left ventricle, *MPO* myeloperoxidase, *NHL* non-Hodgkin lymphoma, *NT-proBNP* N-terminal fragment B-type natriuretic peptide, *TnI* troponin I, *TZT* trastuzumab

solved, including the optimal timing of assessing, frequency of cTn evaluations, optimal cut-off point for positivity with the highest level of specificity, and comparison of different assays of troponin [49]. Table 12.2 reports main studies which demonstrated usefulness of TnI for predicting CTX.

Natriuretic peptides are hormones released during haemodynamic stress when ventricles dilate, undergo hypertrophy, or is subject to increased wall tension. Use of BNP and NT-proBNP to detect subclinical cardiac dysfunction is under investigation, and results of published studies are controversial [54, 62, 63].

BNP levels were increased during chemotherapy treatment and correlated with diastolic dysfunction [55] and progressive development of cardiac dysfunction [56, 64].

In some studies, BNP anomalies were observed in the absence of changes in cTn [57, 65, 66], which suggested that in patients receiving anticancer drugs at low or medium doses and with a predictable reduced myocardial suffering, BNP monitoring could be more useful than cTn [49]. In other studies, BNP was not predictive of EF change [28].

Other *circulating biomarkers* tested include C-reactive protein, cytokines, and parameters of oxidative stress.

Due to the mechanisms of anthracycline-mediated toxicity, measurement of inflammatory markers and parameters of oxidative stress are also reasonable [49, 58]. *C-reactive protein* is a nonspecific marker of inflammation, and the utility of its evaluation in the setting of anticancer drug-related CTX is controversial.

Recently, *galectin-3* (gal-3) has been considered as a potential biomarker for predicting early or late onset of CTX. However, increases of gal-3 were found to be insignificant and not predictive of CTX as defined by echo-derived LVEF reduction [53].

Finally, potential CTX markers under investigation in oncology are heart-type fatty acid-binding protein (H-FABP), glycogen phosphorylase BB (GPBB), and circulating microRNAs, but they are not yet validated [59–61].

Multimodality Approach

As demonstrated by recent studies, a combined multimodality approach in selected individuals may provide incremental value in predicting cardiotoxicity and prove to be useful in clinical practice [28, 53, 67–69]. However, only a few studies have explored the utility of a multimarker approach in monitoring patients undergoing antineoplastic drugs at high baseline risk.

Fallah-Rad et al. [43] conducted the first multimodality surveillance strategy, combining biomarkers (troponin T, CRP, and BNP) with imaging (echocardiography and CMR) in breast cancer patients treated in the adjuvant setting by anthracyclines and trastuzumab. Biomarkers were not associated with any prognostic value, along with LVEF assessment, but Doppler measurement of *s′*, GLS, and radial strain parameters were able to identify, at 3 months' follow-up, the patients who developed CTRCD at 6 months. In this study, CMR, performed at baseline and at 12 months, documented an increase in LV volumes, a decrease in LVEF, and a late gadolinium enhancement in the LV lateral wall in the CTRCD group.

Similarly, Sawaya et al. [18] observed that NT-proBNP was not associated with any predictive value, while high-sensitive TnI at 3 months appeared as an independent predictor of cardiotoxicity at 6 months. Furthermore, a combination of GLS and hsTnI allowed with a better accuracy the early identification of myocardial damage and was predictive of subsequent CRTCD during the surveillance in patients receiving trastuzumab after anthracyclines.

The troponin levels added prognostic value to GLS: if both were abnormal, the specificity for the prediction of CTRCD increased from 73% to 93%. If both were normal, the negative predictive value increases to 91% [28].

Given these scientific evidences, the recent EACVI/ASE consensus document [15] encourages an integrated approach to early detect cardiotoxicity. Particularly a strategy that includes, in addition to LVEF assessment, the calculation of GLS and the measurement of troponin at baseline and during follow-up in order to compare changes during time is proposed. (Fig. 16.4).

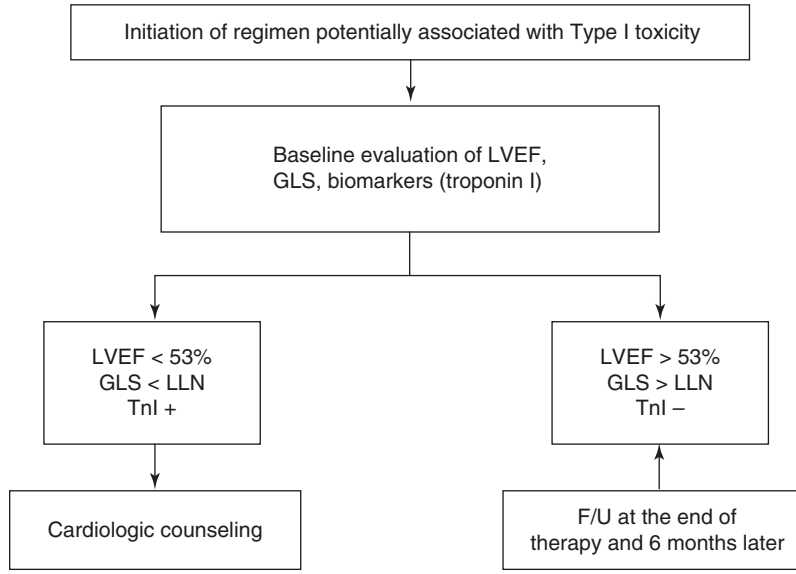

Fig. 16.4 Multimodality approach to monitor patients undergoing antineoplastic treatment. 2DE, 2D echocardiography; 3DE, 3D echocardiography; GLS, global longitudinal strain; LLN, lower limit of normal; LVEF, left ventricular ejection fraction. (Reprinted from Plana et al. [15]. With permission from Elsevier)

Conclusions

Systematic and repeated monitoring of LVEF remains the most used technique to diagnose cardiotoxicity in clinical practice. 2DE is the most used method; however, 3DE has proved to be more accurate and reproducible, and this is preferable if available. Regarding CMR, it is very accurate, but its low availability and the high cost limit its use to particular subsets of patients.

Decrease of LVEF is detectable when damage is considerable and possibility of recovery reduced; therefore it is not suitable as an early indicator of cardiotoxicity.

Among the new techniques that evaluate cardiac function, GLS derived by 2D-STE is the best validated technique with a considerable amount of evidences supporting its role in the detection of cardiotoxicity. Baseline evaluation of GLS and periodical monitoring during treatment is recommended. Promising techniques such as 3D-STE and tissue characterization performed by CMR are under investigation and could provide new insights into the future for the evaluation of chemotherapy-treated patients.

Monitoring troponin levels also appears to be effective in the prediction of cardiotoxicity, and its elevations identify high-risk cohort of cancer patients who may benefit from early cardioprotective medication. According to some evidences, the persistence of NT-proBNP elevation seems to identify patients at higher risk of LVEF decline.

A multimodality approach using troponin and GLS seems to increase the accuracy in the detection of cardiotoxicity especially in patients at high baseline risk; however further studies are needed for wider validation in the clinical setting.

Cardiotoxicity is likely to be a continuous phenomenon characterized by progressive left ventricular ejection fraction decline that, if disregarded and not treated, may progressively lead to overt heart failure. On the other side, if we catch this process in the early phases, overt damage can be prevented and the dysfunction avoided. For this reason, it is extremely important to monitor patients undergoing antineoplastic drugs and to apply sensitive technique to early detect damage.

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