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Echocardiography and biomarkers for the diagnosis of cardiotoxicity

Introduction

Advances in cancer treatment have led to a significant improvement in the prognosis of patients with malignant diseases. However, cardiotoxic side effects can significantly limit the quality of life and survival of tumor patients during and after therapy. The clinical spectrum of cardiotoxicity is very broad and ranges from heart failure and cardiomyopathies over valve diseases, ischemia, pericardial diseases, and hypertension to arrhythmias (**Table 1**). As cardiomyopathy and heart failure are the most common and often most limiting manifestations [1], this review will mainly focus on those conditions.

The fact that cardiac dysfunction can arise from cancer therapy was first described in the 1960s after anthracyclines were introduced into cancer therapy [2]. As a result, increasing attention has been paid to the occurrence of heart failure as a relevant side effect of cancer therapy. In addition to the determination of left ventricular ejection fraction (LVEF) by echocardiography, endomyocardial biopsy was initially of great value in the diagnosis of cardiotoxicity. The latter lost its importance due to major advances in cardiac imaging and the introduction of biomarkers for the early detection of cardiac damage [3]. Echocardiography and biomarkers are fast, safe, and widely available methods for assessing cardiac damage, especially when evaluated serially during potentially cardiotoxic chemotherapies. In the following, the importance of echocardiography and the benefits of determining biomarkers in the context of the diagnosis of cardiotoxic effects will be described in more detail.

The gold standard of evaluation of left ventricular (LV) function, volume, and masses is still cardiovascular magnetic resonance (CMR) imaging. CMR provides superior reproducibility of LVEF and the detection of small changes in LVEF and volumes compared to echocardiography [4]. Nevertheless, its use in clinical practice is limited by costs and limited availability.

Definition of cancer therapeutics-related cardiac dysfunction (CTRCD)

In 2014, the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) presented a concordant expert consensus defining CTRCD as a "decrease in the LVEF of >10 percentage points to a value <53% (normal reference value for two-dimensional [2D] echocardiography [2DE]). This decrease should be confirmed by repeated cardiac imaging […] performed 2 to 3 weeks after the diagnostic study showing the initial decrease of in LVEF" [3]. It must be emphasized that, currently, CTRCD is defined differently by several scientific communities (e.g., European Society of Cardiology, European Society of Medical Oncology, National Cancer Institute, etc.) [5], which leads to difficulties in comparing and harmonizing the results across studies. Various authors have suggested a standardization of the definition.

Two different forms of CTRCD are distinguished based on the underlying mechanism [3]:

1. Type I CTRCD—typically caused primarily by anthracyclines (doxorubicin, epirubicin, and idarubicin), but also by mitoxantrone, leads to an irreversible cardiac muscle cell damage that depends on the cumulative dose. The extent depends, among others, on pre-existing cardiac impairment. This form of damage has a high potential for long-term irreversible cardiac impairment, increased morbidity, and mortality.
2. CTRCD type II—caused by several different agents (e.g., trastuzumab), more likely to lead to non-dose-dependent and reversible damage to the heart muscle.

CTRCD is a leading reason for morbidity and mortality in cancer survivors. The mortality rate for patients with CTRCD is reported to be up to 60% within the first 2 years after treatment [6]. While cardiotoxic effects of anthracyclines and trastuzumab are well-known, it must be emphasized that many of the newer targeted therapies, including tyrosine kinase inhibitors and modern immunotherapies, can also lead to cardiac dysfunction [4].

In patients with an increased cardiovascular risk, the initial assessment of cardiac structure and function before the start of potentially cardiotoxic cancer treatment is of crucial importance

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Table 1 Types of cancer therapy and their associated cardiotoxicity risk. The risk assigned to each treatment represents an overview of the overall risk associated with that class of chemotherapy treatment; however, drug-specific risk within each category may lie outside the range listed. From Seraphim et al. [4] licensed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

Cancer therapy	LVD	Myocarditis	Hypertension	Valve disease	Coronary spasm	Coronary thrombosis	Atherosclerosis	Pericardial constriction	Pericardial effusions	Pulmonary HTN	QT-prolongation	Arrhythmia	Conduction disease
Anthracyclines	+++								+			+	
HER2 monoclonal antibodies	+++												
VEGF monoclonal antibodies	++		+++			++							
BCR-ABL tyrosine kinase inhibitors	++*	++*		++*			++*	++*	++*				
VEGF tyrosine kinase inhibitors	++		+++			++					+++		
Bruton kinase inhibitor			++									++	
Immune checkpoint inhibitors	++	++											
Proteasome inhibitors	++	++	+++			++				++			
Fluoropyrimidines					+++	++						+	
Arsenic trioxide									+++		+++		
Alkylating agents	++					++			+	+			
All-transretinoic acid									++				
Immunomodulatory drugs (myeloma)	++					++						++	
Radiotherapy (mantle/high dose)	++		+++	+++			+++	++					++
Radiotherapy (low dose)			++	++			++						

+++ Treatment associated with >10% risk of developing that form of cardiotoxicity; ++ risk is estimated to be between 1 and 10%; + risk estimated to be <1%

BCR-ABL breakpoint cluster region Abelson murine leukemia viral oncogene homolog, *HER2* human epidermal growth factor receptor 2, *HTN* hypertension, *LVD* left ventricular dysfunction, *VEGF* vascular endothelial growth factor

*Drug-dependent risk

to assess the risk before treatment and enable better classification of possible pathologies during therapy [3, 7–9].

The workhorse of imaging: echocardiographic evaluation of cancer patients

Echocardiography still plays a central role in the diagnosis of CTRCD. It allows the evaluation of the left and right ventricular dimensions, volumes, and functions, as well as the valves and pericardial and large vascular pathology. The advantages of echocardiography lie in its low costs, widespread availability, simple assessment of serial examinations in the course of the disease or during therapy, and no exposure to ionizing radiation [3, 4]. However, the informative value of this methodology is essentially limited by the dependence on the individual acoustic window (limited, e.g., after mastectomy) and by the known inter- and intra-observer variability. Especially in terms of the determination of LV function, two-dimensional echocardiography (2DE) has a limitation due to its dependence on geometric assumptions [4].

To assess cardiac damage, LVEF, or more precisely 2D LVEF, is the main marker of cardiac dysfunction that has been used in clinical practice and research in recent decades. Early asymptomatic decreases are associated with a later progression to clinical heart failure associated with cancer treatment [10–12]. The prognostic value of reduced LVEF is unquestionable [1]. Serial imaging is therefore recommended before, during, and after treatment with anthracycline or other cardiotoxic agents.

In addition to image quality, the reliable detection of CTRCD also crucially depends on the extent to which subtle changes in LVEF are recognized as such. The current recommendations endorse the modified biplane Simpson's technique by 2DE as the standard method for LVEF determination [3]. However, the test–retest variability in LVEF measurement using 2D echocardiography is up to 10% [13]. Furthermore, sensitivity for the detection of small changes in LV function is low and calculated 2D LVEF often fails to detect small changes in LV contractility [3]. This raises the question of whether this method is suitable for early and reproducible detection of CTRCD. By using transpulmonary contrast medium, precision can be increased compared to isolated 2DE—especially in patients with a poor acoustic window [14].

In addition, the measurement of LVEF depends on the loading conditions: different loading conditions can influence the value (e.g., volume overload during

Abstract · Zusammenfassung

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Abstract

As a result of better treatment options for malignant cancer, the cardiovascular side effects of such therapies have increasingly come into focus in recent years. The new cardiological subspecialty of oncocardiology is developing strategies to prevent and/or detect those effects early in order to treat them in a timely and adequate manner. The diagnosis of cardiotoxic effects is based mainly on imaging and specific biomarkers. Echocardiography has become the main imaging technique due to its wide availability. In addition to quantitative determination of left ventricular function using two-dimensional methods, three-dimensional methods offer better precision and less variability in the detection of cardiac dysfunction. Furthermore, the analysis of the global longitudinal strain (GLS) reveals even subtle changes in left ventricular function and thus detects very early damage before left ventricular ejection fraction drops. Various biomarkers have been tested recently for their potential to detect cardiotoxicity. Cardiac troponins are currently the best investigated biomarkers and certainly have the highest impact. Due to contradicting results, the importance of natriuretic peptides has not yet been conclusively clarified. Results for myeloperoxidase are promising, as are the results for circulating microRNAs, which still mainly derive from experimental data. In this context, further studies still need to show the value of these in everyday clinical practice.

Keywords

Oncocardiology · Imaging · Global longitudinal strain · Troponin · Natriuretic peptides

Echokardiographie und Biomarker zur Diagnose der Kardiotoxizität

Zusammenfassung

Als Folge einer besseren Therapie von malignen Tumorerkrankungen treten in den letzten Jahren zunehmend die kardiovaskulären Nebenwirkungen der Tumortherapien in den Fokus. Die neue kardiologische Subspezialität der Onkokardiologie entwickelt Strategien, diese frühzeitig zu erkennen, um sie rechtzeitig und adäquat therapieren zu können. Die Diagnose kardiotoxischer Effekte basiert dabei auf der Bildgebung und spezifischen Biomarkern. Aufgrund der breiten Verfügbarkeit stellt die Echokardiographie das wichtigste bildgebende Verfahren dar. Neben der quantitativen Bestimmung der linksventrikulären Funktion mittels 2-D-Methoden bieten 3-D-Techniken eine bessere Präzision und geringere Variabilität in der Detektion einer kardialen Dysfunktion. Die Bestimmung des „global longitudinal strain" (GLS) hilft, auch subtile Änderungen der linksventrikulären Funktion zu detektieren und sehr frühe Schädigungen festzustellen, bevor diese sich in der linksventrikulären Ejektionsfraktion niederschlagen. In den vergangenen Jahren sind verschiedene Biomarker zur Detektion von Kardiotoxizität geprüft worden. Am besten untersucht und sicherlich den größten Nutzen bieten aktuell die kardialen Troponine. Der Stellenwert der natriuretischen Peptide ist aufgrund widersprüchlicher Ergebnisse noch nicht abschließend geklärt. Ergebnisse zur Myeloperoxidase sind vielversprechend – ebenso wie die aktuell vorwiegend noch experimentellen Daten zu microRNAs. Hier müssen weitere Studien den Stellenwert für den klinischen Alltag zeigen.

Schlüsselwörter

Onkologische Kardiologie · Bildgebung · „Global longitudinal strain" · Troponin · Natriuretische Peptide

chemotherapy or volume depletion due to nausea, vomiting, and diarrhea) [3].

Three-dimensional echocardiography (3DE) offers a more precise way of measuring LV volumes [15]. A recent study [13] showed that 3DE without contrast medium showed the least variability in measurements compared to 2D methods. 3DE also had the best intra- and interobserver and test–retest variability. Therefore, if available, 3DE is the method of choice for serial monitoring of cardiac effects of chemotherapy [16]. Disadvantages of this methodology are its higher costs, lower availability, and high demands on image quality, not to forget the appropriate expertise of the examiner. The combination of 3DE with contrast agent in patients with cancer showed less reproducibility and greater temporal variability compared to 3DE without contrast agent [13] and is not recommended [3].

Detection of subclinical LV dysfunction

In comparison to other causes of heart failure, the prognosis of anthracycline-related cardiomyopathy is significantly worse [17]. Therefore, early diagnosis is of central importance. If a drop in LVEF is detected, the possibility of an optimal intervention may already have been missed [4]. Cardinale et al. showed that an early start of therapy with enalapril and, when possible, carvedilol was associated with an improvement in LVEF. In contrast, late intervention was associated with poor cardiac function or lack of recovery [18]. Data from a trial including 2625 patients with anthracycline-based chemotherapy showed an incidence of 9% cardiotoxicity. In 98% of the patients, cardiotoxicity occurred within the first 12 months after treatment [19]. In addition, a study that compared histopathological findings with the LVEF determination showed no association between histologically demonstrable damage and LVEF decline. The deterioration in LVEF appears to be a relatively late marker [20]. Therefore, further research should notably aim to identify alternative markers that indicate early damage before a decline in LVEF or clinical symptoms occur. In this context, several approaches including diastolic function parameters have been studied. Strain imaging has emerged as the most promising tool for the detection of early, subtle functional deterioration.

The role of strain imaging in cardiooncology

The early detection of subclinical LV dysfunction plays a crucial role in delaying or even preventing the occurrence of overt heart failure in patients during potentially cardiotoxic chemotherapy. However, detection of such subclinical dysfunction can be a considerable challenge [6]. Global longitudinal strain (GLS) by 2D speckle tracking echocardiography emerged as a sensitive marker for early mild abnormalities in myocardial functionality [1] and may predict future cardiotoxicity and decline in LV function [21, 22]. In detecting subclinical changes, GLS calculation is superior to the conventional echocardiographic parameters such as LVEF. A relative reduction of GLS by 10–15% is an early predictor of subsequent cardiotoxicity [21, 23]. Thus, the determination of GLS in cancer patients undergoing cardiotoxic therapies is recommended by international associations for echocardiography (ASE, EACVI), as well as by the American Society for Clinical Oncology (ASCO) [3, 9]. Furthermore, a recent study showed that interobserver agreement of GLS was better than for LVEF in patients undergoing potentially cardiotoxic chemotherapy [24]. In the 2016 ESC position paper on cancer treatments and cardiovascular toxicity, the authors stated that for patients with an asymptomatic reduction of GLS during chemotherapy there is currently "no evidence to guide specific cardioprotection" and that "based on currently available evidence, cancer treatment should not be stopped, interrupted or reduced in dose based on a new GLS reduction alone" [8]. The ongoing SUCCOUR trial [25] is the first randomized controlled trial to use GLS as a predictive biomarker for CTRCD. Patients undergoing potentially cardiotoxic chemotherapy are randomized to a GLS-directed vs. a LVEF-directed approach. The results of this study will have a decisive impact on the importance of GLS in clinical practice. Recently, it has been shown that a decrease in GLS also predicts myocarditis in patients receiving immune checkpoint inhibitors (ICI) [26].

Current guidelines recommend the comparison of GLS measured during chemotherapy cycles with baseline GLS values. A relative reduction <8% compared to baseline values does not seem to be meaningful, whereas a reduction >15% seems to be abnormal [3]. As the strain values are vendor and software specific, the same vendor-specific ultrasound machine or software should ideally be used in the follow-up of patients. If GLS is not available, at least mitral annulus plane systolic excursion (MAPSE) and tissue doppler imaging (TDI) should be determined according to EACVI recommendations [3].

Furthermore, 3D-GLS was shown to detect cardiotoxicity earlier than 2D-GLS, suggesting that 3DE may provide more sensitive detection of cardiac dysfunction [27, 28]. Further studies need to address the impact of 3D-GLS in the assessment of cardiotoxicity.

Biomarkers

Several biomarkers have been tested for the detection and management of cardiotoxicity and as an alternative or addition to imaging. The cardiac biomarkers most intensely studied include cardiac troponins (Troponin I and Troponin T) and natriuretic peptides.

Troponin

As markers of myocardial injury reflecting damage to myofibrils and cardiomyocytes, cardiac troponins are extensively studied in the setting of cardiotoxicity. As early on as in 2000, Cardinale et al. [29] published a study on troponin I (TnI) in patients receiving high-dose chemotherapy. Of 204 patients, 65 had elevated TnI values. The authors were able to show that a TnI increase was a predictor of future deterioration in LVEF. TnI is therefore a sensitive marker for early cardiotoxic damage.

In another study including 703 patients [30], TnI values were recorded within 72 h after high-dose chemother-

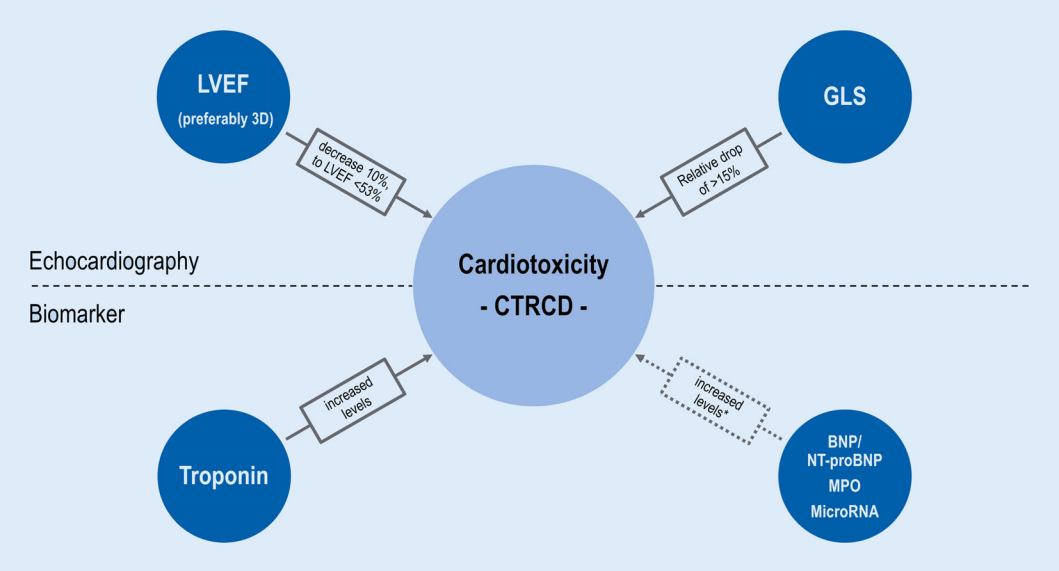

Fig. 1 ▲ Overview of different markers (possibly) indicating cardiotoxicity. Whereas cancer therapeutics-related cardiac dysfunction (*CTRCD*) is defined by the change in left ventricular ejection fraction (*LVEF*), other echo parameters like global longitudinal strain (*GLS*) as well as several biomarkers may also indicate sub-clinical left ventricular dysfunction. Data on the GLS and the myocardial injury indicating biomarker troponin are relatively strong. However, data on natriuretic peptides have revealed conflicting results. The impact of other/modern biomarkers in clinical practice need to be defined by further studies. *Might indicate/conflicting results; *3D* three-dimensional, *BNP* b-type natriuretic peptide, *CTRCD* cancer therapeutics-related cardiac dysfunction, *GLS* global longitudinal strain, *LVEF* left ventricular ejection fraction, *MPO* myeloperoxidase, *NT-proBNP N*-terminal pro-BNP

apy and 1 month later. Persistently elevated TnI values indicated a significantly increased risk of cardiovascular events in contrast to patients with only initially increased TnI values (84% versus 37% of the patients). The risk of cardiovascular events was only 1% in patients being TnI-negative at both time points. Increased TnI also predicts the occurrence of cardiotoxic side effects during trastuzumab therapy. Recovery of cardiac dysfunction during heart failure drug therapy is also less likely in patients that are TnI-positive [31]. These results suggest that determination of TnI potentially helps to identify patients receiving high-dose chemotherapy that are at high risk of cardiovascular events [32].

In contrast, another study failed to identify TnI as an early predictor of cardiac dysfunction in women with HER2-positive breast cancer with low-dose anthracycline therapy and trastuzumab [23]. However, due to its high negative predictive value, TnI seems to be suitable for identifying patients with a low risk of cardiovascular events [33]. As a consequence, in patients with elevated values, more intensive monitoring may be recommended, while the ideal timing for TnI analysis is still unclear. The cut-off for "positive" was also chosen differently in the studies and is not defined homogeneously. Besides various treatment regimens used in the trials, this is certainly also a reason for the conflicting results [32]. A recent meta-analysis [34] of cardiac biomarkers in CTRCD including 61 studies underlined the impact of troponin in the detection of cardiotoxicity. In this analysis, patients with elevated troponin had a relevantly elevated risk for LV dysfunction compared to troponin-negative patients (odds ratio [OR] 11.9, 95% confidence interval [CI] 4.4–32.1) with a negative predictive value of 93% [34].

A more accurate prognostic value can be achieved by combining TnI with imaging parameters. GLS and ultrasensitive TnI measured at the completion of anthracycline treatment predicted subsequent development of cardiotoxicity. By combining an increase of TnI with a decrease of GLS below 19% improves sensitivity up to 87% (GLS alone 74%, TnI alone 48%) [21].

In patients receiving ICI, myocarditis is found in 1–2%, typically occurring during the first 3 months after initiation of the ICI therapy and associated with a high mortality rate of 43–46%. Elevated troponin can be found in more than 90% of patients with ICI-induced myocarditis [35].

Natriuretic peptides

The natriuretic peptides B-type natriuretic peptide (BNP) and the *N*-terminal end of its precursor hormone NT-proBNP are released in response to volume overload or increased wall stress. They play an important role in the diagnosis of heart failure [36]. BNP and NT-proBNP were also examined for predicting cardiotoxicity in cancer patients receiving chemotherapy. However, there are some conflicting results: Skovgaard et al. showed that increased BNP (>100 pg/mL) predicted overt heart failure in a cohort of 333 patients treated with cardiotoxic chemotherapy [37]. Romano et al. showed that a sustained increase in NT-proBNP was predictive of a deterioration in LVEF during an-

thracycline-based chemotherapy [38]. In contrast to the above, another study by Dodos et al. revealed that a transient increase in NT-proBNP was not associated with a change in LV function [39]. In a study by Sawaya et al., NT-proBNP was not a predictor of cardiotoxicity [21]. The above-mentioned meta-analysis revealed that neither BNP nor NT-proBNP were able to consistently predict LV dysfunction (OR 1.7, 95% CI 0.7–4.2) [34].

In summary, there is clearly a need for further prospective studies to clarify the importance of biomarkers such as troponin or natriuretic peptides and their correct use and interpretation (optimal time of determination, cut-offs, etc.).

Other biomarkers

Some other biomarkers have been evaluated in the setting of cardiotoxicity. In a multimarker approach, Ky et al. tested eight biomarkers in patients undergoing doxorubicin and trastuzumab therapy [40]: ultrasensitive TnI (cardiomyocyte injury), high-sensitivity C-reactive protein (CRP) (inflammation), NT-proBNP (neurohormonal activation), growth differentiation factor (GDF)-15 (inflammation and oxidative stress), myeloperoxidase (MPO) (oxidative stress), placental growth factor (PlGF) (angiogenesis), soluble fms-like tyrosine kinase receptor (sFlt)-1 (vascular remodeling), and galectin (gal)-3 (fibrosis). Only early changes in TnI and MPO were associated with subsequent cardiotoxicity [40]. The combination of both biomarkers provided additional value. MPO is released from neutrophil granulocytes and is considered a biomarker for oxidative stress, which is regarded as one of the basic mechanisms in cardiac damage by anthracyclines. During follow-up after termination of anthracycline treatment, the predictive value of an increase in MPO levels was maintained [41]. Data on troponin were confirmed in a very recent multicenter study [42] on 323 patients undergoing therapy with anthracyclines and/or trastuzumab: elevated high-sensitivity cardiac troponin T at the time of completion of anthracycline therapy was associated with a two-fold increase in CTRCD risk. MPO increase was associated with CTRCD in patients receiving sequential anthracyclines and trastuzumab. Significant associations with changes in LVEF or CTRCD were neither shown for PIGF nor for GDF-15. Changes in NT-proBNP were associated with very modest changes in LVEF and with the occurrence of CTRCD.

In recent years, microRNAs (small, non-coding RNA molecules that play an important role in the regulation of gene expression) were also analyzed regarding their potential to predict cardiotoxicity. While most of the results derive from experimental data, some findings have already been confirmed in patients [43]. For example, miR-1 was upregulated in breast cancer patients treated with doxorubicin. The levels of miR-1 were associated with changes in LVEF over time and predicted the occurrence of cardiotoxicity [44]. Furthermore, the predictive value of miR-1 outperformed TnI. From experimental data, the following microRNAs might play a role as biomarkers in detecting cardiotoxicity: miR-200 family, miR-34 family, miR-29 family, miR-30 family, miR-21, miR-1, miR-133, miR-208a/b, miR-499, miR-221/222, and miR-320a [43]. Further clinical trials are needed to elucidate the impact of miRNAs on cardiotoxicity and translate experimental data into clinical practice.

Myocardial ischemia

Beside the effects on LV function in terms of CTRCD, some cancer therapies are associated with the occurrence of myocardial ischemia (**Table 1**; [8]), e.g., 5-fluorouracil, gemcitabine, bevacizumab, sorafenib, and sunitinib [3, 8]. However, myocardial ischemia also occurs as a result of radiation. Analogous to diagnostics in non-cancer patients, stress echocardiography can provide valuable diagnostic support in those patients. In addition, the risk of myocardial ischemia increases significantly with these therapies in the case of pre-existing coronary heart disease [8]. Therefore, in patients with an intermediate or high pre-test probability for coronary heart disease, stress echocardiography might be useful before initiation of antineoplastic therapies [3].

Conclusion

Advances in cancer therapy have led to a significant improvement in prognosis, which is adversely affected by the occurrence of cardiotoxic side effects. The early detection of such side effects therefore plays an important role (**Fig. 1**). Changes in LVEF occur relatively late, and a later onset of appropriate cardioprotective therapy is associated with poorer response. Modern parameters such as GLS by 2DE, as well as biomarkers, especially troponin, may detect cardiotoxic damage at an early stage. Further studies especially with regard to biomarkers still need to define the optimal timing for determination and cut-offs. Modern biomarkers such as myeloperoxidase or microRNAs represent promising new approaches that still need to be evaluated in clinical studies to define their value for clinical practice.

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Compliance with ethical guidelines

Conflict of interest. D. Berliner, G. Beutel, and J. Bauersachs declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors.

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