Cardiotoxicity of anthracycline-free targeted oncological therapies in HER2-positive breast cancer (Review)

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Abstract. Anthracycline drugs are considered to be pivotal drugs in numerous chemotherapy regimens for breast cancer. However, the cardiotoxicity associated with the treatment is an important issue to be addressed. With the emergence of increasingly diverse antitumor drugs, anthracycline-free therapies are able to reduce the cardiotoxicity caused by anthracycline drugs while ensuring that a therapeutic effect is achieved. In the present review, anthracycline-free oncological therapy regimens for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer and the associated cardiovascular toxicity are discussed, as well as some monitoring strategies. It is recommended that patients with HER2-positive breast cancer patients should receive adjuvant chemotherapy with single or dual-targeted therapy, with or without endocrine therapy according to the hormone receptor status determined by immunohistochemical examination. The main side effects of targeted therapy include cardiac dysfunction, hypertension and arrhythmia. According to individual risk stratification, it is recommended that patients should be periodically monitored using echocardiography, electrocardiography and serum markers, to enable the timely detection of the cardiovascular adverse reactions associated with tumor treatment, thereby preventing the morbidity and mortality caused by the cardiotoxicity of these drugs.

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Abbreviations: HER2, human epidermal growth factor receptor 2; DFS, disease-free survival; pCR, pathological complete response; LVEF, left ventricular ejection fraction; EGFR, epidermal growth factor receptor; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor; EDI, ERK-dimerization inhibitory; ECG, electrocardiogram; CMRI, cardiac magnetic resonance imaging; ESC, European Society of Cardiology; ASE, American Society of Echocardiography; GLS, global longitudinal strain; 2D, 2-dimensional; 3D, 3-dimensional; 3DE, 3D echocardiography; TDI, tissue Doppler imaging; STE, speckle-tracking echocardiography; RV, right ventricular; NT-proBNP, N-terminal pro-brain natriuretic peptide; CTRCD, chemotherapy-related cardiotoxicity; HF, heart failure; sST2, soluble suppression of tumorigenicity 2; hs-cTnI, high-sensitivity cardiac troponin I

Key words: cardiotoxicity, anthracycline-free, breast cancer, surveillance

Contents

1. Introduction

Anthracycline-based chemotherapy regimens like doxorubicin and cyclophosphamide followed by docetaxel (AC-T) or AC-T + trastuzumab (AC-TH) play a prominent role in the treatment of breast cancer, and contribute to the global 5- and 10-year survival rates of 73 and 61%, respectively, for female patients (1). Unfortunately, the administration of these regimens has been limited due to the increased risk of irreversible cardiotoxicity associated with anthracyclines, with cardiac dysfunction and arrhythmia as the main adverse reactions. The long-term cardiotoxic effects of chemotherapy (2), which may lead to increased cardiovascular morbidity and mortality, account for the majority of deaths of patients with cancer from non-tumor causes (3).

For patients who have metastatic breast cancer, are older or have other underlying diseases, anthracycline drugs are not suitable because of their high toxicity. Therefore, the identification of alternatives to anthracyclines that are equally effective is important. In the phase III Breast Cancer International Research Group 006 study on patients with human epidermal

growth factor receptor 2 (HER2)-positive breast cancer with axillary lymph node involvement or high-risk negative cancer, the cardiotoxicity in patients treated with docetaxel, carboplatin and trastuzumab (TCH) was lower than that in patients treated with AC-T or AC-TH. Both disease-free survival (DFS) and overall survival were significantly improved in the patients treated with TCH, the cardiotoxicity rates of which were also reduced compared with those of the other treatments; the rates of congestive heart failure (CHF) events in the TCH, AC-TH, and AC-T groups were 0.4, 2.0 and 0.7%, respectively (4,5). From other trials in which anthracycline-containing therapy was compared with anthracycline-free therapy (Table I), it is evident that the cardiotoxicity of anthracycline-free regimens is lower than that of anthracycline-containing regimens, but is not negligible.

The present review describes the current epidemiological evidence on the cardiotoxicity associated with anthracycline-free therapy, particularly targeted drugs, in patients with HER2-positive breast cancer, as well as the clinical manifestations, possible mechanisms and achievable clinical monitoring recommendations for the therapies. Since there are few retrospective clinical studies on the treatment of the cardiovascular complications associated with cancer therapy, the discussion of clinical monitoring in this review represents the opinions of the authors based on currently available information.

2. Epidemiology

At present, in patients with HER2-positive breast cancer, if no contraindications are present, the use of anti-HER2 targeted drugs is advocated. The National Comprehensive Cancer Network guidelines recommended that patients with HER2-positive breast cancer receive adjuvant chemotherapy with single or dual targeted therapy, with or without endocrine therapy according to hormone receptor status determined by immunohistochemical examination (6). However, evidence of cardiovascular toxicity secondary to neoadjuvant or adjuvant therapy in HER2-positive breast cancer has emerged in a trial involving HER2 blockade (7). With regard to the molecular mechanism, the activity of ErbB proteins in normal cells relies on heterodimer formation; the heterodimer formed between HER2 (also known as ErbB2) and ErbB3 induces the proliferation in breast tumor cells, and the heterodimer formed between HER2 and ErbB4 is key to the proliferation and contractility of cardiac myocytes (8). The anti-HER2 agent trastuzumab inhibits HER2-induced intracellular signaling and marks HER2-positive cells for antibody-dependent cellular cytotoxicity by binding to the extracellular structure of HER2 in cancer cells as well as cardiomyocytes (9). This leads to significantly improved DFS in women with HER2-positive breast cancer but also increases the risk of severe cardiotoxicity (10).

A retrospective study showed that 13% of patients with metastatic breast cancer who were treated with trastuzumab plus paclitaxel had cardiac dysfunction (11). In other studies, the combination of trastuzumab and pertuzumab significantly increased progression-free survival and pathological complete response (pCR) in patients with breast cancer without affecting the incidence of cardiotoxicity (12-15). In the NeoSphere study (13), 45.8% of the patients treated with neoadjuvant trastuzumab and pertuzumab combined with chemotherapy achieved a pCR, compared with 29.0% of the patients treated with chemotherapy combined with single-agent trastuzumab. Among patients treated with pertuzumab, trastuzumab, and docetaxel, only 3/107 patients (3%) showed a decline of 10-15% in the left ventricular ejection fraction (LVEF) from the baseline. In a 5-year analysis of the NeoSphere study, cases of left ventricular dysfunction of grade 3 or worse were followed up, and it was found that the majority of the asymptomatic LVEF reductions of ≥10% occurred during adjuvant trastuzumab therapy (16). A 2013 meta-analysis (15) of six trials in patients with breast cancer showed that the incidence of serious cardiovascular events in patients treated with dual anti-HER2 agents was similar to that of patients treated with anti-HER2 monotherapy, and the absolute incidence of each cardiac event was relatively low (CHF, 0.88%; LVEF decline 3.1%). This result is inconsistent with that of the PERTAIN trial, a randomized, phase II trial in which left ventricular dysfunction was observed in 3 (2.4%) patients in the pertuzumab plus trastuzumab arm but none in the trastuzumab arm (17). These conflicting results may be attributed to the different mechanisms by which pertuzumab and trastuzumab act. Pertuzumab binds to the extracellular domain II of HER2, which inhibits the formation of HER2 heterodimers and consequently affects activation of the HER2 signal pathway, while trastuzumab binds to the juxtamembrane region (domain IV) of HER2, inducing receptor dimerization and activation of the cytoplasmic kinase, which subsequently leads to autophosphorylation and initiation of downstream signaling events (18-20).

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate of trastuzumab that targets the microtubule inhibitor emtansine to HER2-overexpressing tumor cells. T-DM1 decreases the risk of recurrence of invasive breast cancer to a greater extent than trastuzumab alone. However, the toxicity of T-DM1 is also higher than that of trastuzumab (21). A pooled analysis of T-DM1 trials showed that T-DM1-mediated cardiotoxicity occurred early, with approximately half of the cardiac events occurring within the first 100 days of treatment, and demonstrated that older people tended to be more vulnerable, with a 5% increase of cardiac risk per 1-year increase in age (22). In the KATHERINE trial, the incidence of hypertension in the patients treated with T-DM1 was 2.0% compared with 1.2% in those treated with trastuzumab (21).

With the widespread administration of trastuzumab, drug resistance has been observed in patients with metastatic breast cancer. Lapatinib, which inhibits both HER2 tyrosine kinase and the epidermal growth factor receptor (EGFR), was approved in 2007 for use in combination with capecitabine for the treatment of HER2-positive metastatic breast cancer, with EGFR serving as an alternative target to the HER2 pathway (23). Lapatinib inhibits signaling by binding to Her2-ErbB3 and EGFR complexes (24). A 2017 meta-analysis (25) of 26 lapatinib-containing trials in patients with breast cancer reported that the overall incidence of cardiovascular events was 3.0% (95% CI: 1.50-6.10%), including left ventricular dysfunction (1.7%) and LVEF decline (1.8%). Additionally, as hypertension is the most common manifestation of cardiovascular toxicity it also merits attention. The risk

Table I. Clinical trials comparing anthracycline-based regimens with anthracycline-free regimens.

First author, year	Regimen	Trial	Phase	No. of patients	Study design[a]	Cancer type	Primary endpoint	Cardiac events	(Refs.)
Slamon, 2011	Anthracycline	BCIRG 006	III	1,073	AC^{b}4 → T^{b}4	HER2^{+}, invasive, high-risk, node-negative or node-positive adenocarcinoma	DFS	NYHA III/IV CHF, 0.7%	(5)
				1,074	AC^{b}4 → T^{b}4+H			NYHA III/IV CHF, 2.0%	
	Non-anthracycline			1,075	TCH^{b}6 → H			NYHA III/IV CHF, 0.4% (P<0.001)	
Schneeweiss, 2011	Anthracycline	TRYPHAENA	II	73	FEC+H+P^{b}3 → T+H+P^{b}3	HER2^{+} breast cancer (primary tumor >2 cm)	DFS	LVEF declines ≥10% from baseline to <50%, 11.1%; LVSD 2.8%	(72)
				75	FEC^{b}3 → T+H+P^{b}3			LVEF declines ≥10% from baseline to <50%, 16.0%; LVSD, 4.0%	
	Non-anthracycline			77	TCH+P^{b}6			LVEF declines ≥10% from baseline to <50%, 11.8%; LVSD, 5.4%	
Van Ramshorst, 2018	Anthracycline	TRAIN2	III	219	FEC+H+P^{b}3 → T+Cb+H+P^{b}6	HER2^{+} breast cancer	pCR	Symptomatic LVSD, 1 (1%); hypertension, 5 (2%); LVEF decreased, 4 (2%)	(7)
	Non-anthracycline			219	T+Cb+H+P^{b}9			Symptomatic LVSD, 0; hypertension, 1 (<1%); LVEF decreased, 1 (<1%)	

BCIRG, Breast Cancer International Research Group 006; A, doxorubicin; C, cyclophosphamide; T docetaxel; H, trastuzumab (Herceptin); FEC, 5-fluorouracil + epirubicin + cyclophosphamide; P, pertuzumab; Cb, carboplatin; HER2, human epidermal growth factor receptor 2; DFS, disease-free survival; pCR, pathological complete response; NYHA, New York Heart Association; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction. Study design[a], in this column, ^{b}n indicates n cycles.

ratio of all-grade hypertension of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) was reported to be 3.43 (95% CI: 2.95-3.99; P<0.00001) (15,26). Multiple reports of QT prolongation in patients treated with sunitinib, but not lapatinib, have emerged, which in some cases have been associated with sudden death (27). Tucatinib, an oral, potent, reversible HER2-specific tyrosine kinase inhibitor (TKI) has been used in combination with T-DM1 for the treatment of advanced HER2-positive metastatic breast cancer. In a phase 1b clinical trial, grade 1 heart failure (HF) occurred in 2/50 patients (4%) who received T-DM1 (3.6 mg/kg intravenous infusion every 21 days) and tucatinib (300 mg orally twice daily for 21 days), and one of the patients discontinued the study because of a consistent decline in LVEF (28). TKIs have been shown to inhibit the EGFR/Ras/Raf/MEK/ERK signaling pathway in tumor cells and cardiomyocytes, whereas the Raf/MEK/ERK cascade protects cardiomyocytes from stress-induced damage (29). A recent study revealed that ERK-dimerization inhibitory (EDI) peptide interferes with ERK dimerization and subsequently prevents ERK^{T188} phosphorylation (30). TUNEL assays and measurements of the mitochondrial membrane potential to assess the oxidative stress response *in vitro* and *in vivo* in mice demonstrated the non-cardiotoxicity of EDI. While the membrane potential was depolarized in the presence of all MEK inhibitors tested, EDI protected it from collapse. This intervention has also been shown to effectively inhibit cancer cell proliferation without cardiotoxicity (30). This finding provides new possibilities for the modification of TKIs to reduce or even eliminate cardiotoxicity.

3. Surveillance strategies

Strongly elevated risks of cardiac events have been observed following tumor therapy. Although the benefits of systemic treatments usually outweigh the risks of cardiac events, the need to support ongoing efforts to evaluate preventative strategies should be emphasized. A position paper prepared by the European Society of Cardiology (ESC) recommends that a patient's cardiac condition should be evaluated once per cycle (31). The diagnostic tools proposed for the detection of cardiotoxicity comprise electrocardiograms (ECGs), echocardiography, cardiac magnetic resonance imaging (CMRI) and cardiac biomarkers, including troponin I (TnI), high-sensitivity (hs)-TnI, brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) (31). Based on the evaluation of risk factors for chemotherapy-related cardiotoxicity (CTRCD), there is a growing consensus that the control of relevant risk factors may enable some cardiac events to be avoided (Table II).

ECG. Diagnostic testing with ECG can be nonspecific even if the results are abnormal; however, assessment of the condition of the heart remains essential. The ESC guidelines recommended that each patient should undergo a standard 12-lead ECG examination every treatment cycle, despite studies showing that targeted drug therapy without anthracyclines reduces the risk of arrhythmias, namely tachycardia and bradycardia, and prolongs QT intervals by 40% compared with anthracyclines (31,32).

Table II. Potential cardiac risk factors.

Categories	Risk factors	(Refs.)
Basic factors	Race	(42,73)
	Caucasian	
	African American	
	Female sex	(74)
	Age ≥65 years or perimenopausal	(74,75)
	Tobacco use	(74)
Concomitant disease	Obesity (BMI ≥30 kg/m^2)	(75)
	Diabetes mellitus	(74)
	Cardiovascular disease	
	Baseline LVEF, <55%	(76)
	Heart failure	(74)
	Hypertension	(74)
	Coronary artery disease	(75)
	Peripheral artery disease	(75)
	Hyperlipidemia	(74)
Concomitant therapy	Irradiation of the chest	(74,77)
	Cumulative anthracycline exposure	(74)

BMI, body mass index; LVEF, left ventricular ejection fraction.

There is no evidence of arrhythmia being caused by targeted anti-HER-2 drugs such as trastuzumab and pertuzumab. However, antimicrotubule agents such as paclitaxel can cause arrhythmias, among which asymptomatic bradycardia and first-degree atrioventricular block are the most common types (33). If a patient has any previous risk factors for bradycardia, for example, there is evidence of abnormal cardiac conduction or the long-term use of negative inotropic drug, drugs that may cause arrhythmias should be used with caution and the patient's heart rate should be closely monitored during their use. ECG examination can be performed twice a week if necessary, and medication should be stopped immediately if symptoms or persistent conduction block occurs. In addition, a pacemaker may be implanted if necessary. By contrast, TKIs affect the QT interval, which is typically increased to 15 msec longer than the baseline value; the QT interval-prolonging effects of lapatinib and sunitinib are marked, with average increases of 23.4 and 22.4 msec, respectively, from baseline (34). QT interval prolongation tends to cause malignant arrhythmias, and may even lead to torsades de pointes. Adverse reactions can be graded according to the degree by which the QT interval is prolonged, and different treatments should be given accordingly (Table III). Additionally, it is suggested that electrolytes should be monitored periodically in patients who are highly vulnerable to QT interval prolongation (35).

Echocardiographic measurement. Echocardiography is the most important means of assessing cardiac function during cancer treatment because it is readily available and does not expose the patients to radiation. With regard to the definition of cardiotoxicity, according to guidelines and recommendations issued by the ESC, American Society of Echocardiography (ASE) and European Association of

Table III. QTc prolongation grade and corresponding recommendations.

QTc prolongation grade	Definition	Recommendation[a]
1	Average QTc 450-480 msec	In patients with drug-induced LQTS, removal of the offending agent is indicated (I, A)
2	Average QTc 481-500 msec	In patients with drug-induced LQTS, removal of the offending agent is indicated (I, A)
3	Average QTc ≥501 msec; >60 msec change from baseline	In patients with drug-induced LQTS, removal of the offending agent is indicated (I, A)
4	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	Intravenous magnesium sulfate for patients who take QT-prolonging drugs and present with few episodes of torsades de pointes pacing in which the QT remains long (IIa, B); atrial or ventricular or isoproterenol (IIa, B); potassium ion repletion to 4.5-5 mmol/l (IIb, C)

[a]In the parentheses, the Roman numeral represents the classification of the recommendation, and the letter represents the level of evidence. National Cancer Institute's toxicity definitions for corrected QT interval prolongation (78) and specific treatment recommendations according to the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology (ACC/AHA/ESC) 2006 guidelines (79). LQTS, long QT syndrome.

Cardiovascular Imaging, a >10% reduction in LVEF to a value below the lower limit of normal or a >15% relative reduction in global longitudinal strain (GLS) from baseline is suggestive of cardiotoxicity (31,36). Therefore, it is necessary for patients to undergo an echocardiographic assessment before starting cancer treatment. Patients with a baseline LVEF level of <50% are not suitable for chemotherapy due to their increased risk of cardiac events.

The most important indicator for the assessment of cardiac function is LVEF, which reflects the systolic function of the left ventricle, and can be evaluated using 2-dimensional (2D) and 3-dimensional (3D) echocardiographic acquisitions. The modified biplane Simpson's method is recommended by the ASE for the measurement of LVEF (37). In a study of patients undergoing chemotherapy for breast cancer, for whom comprehensive echocardiograms were performed at five time points by two investigators, 3D echocardiography (3DE) exhibited improved intra- and interobserver as well as test-retest repeatability compared with 2D methods (38), which indicates that 3D measurements can overcome the poor repeatability of echocardiographic measurements of LVEF to a certain extent. Similarly, a 2012 meta-analysis of 23 studies in which 1,638 echocardiograms were performed demonstrated that 3DE is more accurate than 2D methods for the measurement of left ventricular volume and LVEF (39).

Tissue Doppler-derived indices, including systolic (S'), early diastolic and late diastolic velocities, represent different functions of the heart. Tissue Doppler imaging (TDI) is widely recommended for evaluation of the diastolic function of the heart (40). In a study conducted by Fallah-Rad *et al* (41), 42 patients with breast cancer treated with adjuvant trastuzumab were evaluated using TDI. Although the peak global longitudinal and radial strain decreased, 10 patients demonstrated a reduction in lateral S' at 3 months after trastuzumab treatment, and these 10 patients all eventually developed trastuzumab-mediated cardiotoxicity. Retrospective studies have also shown that 20% of patients develop new or worsening diastolic dysfunction during breast cancer treatment (42,43). In the aforementioned studies, the diastolic dysfunction was evaluated by TDI indexes including mitral annular e'velocity (septal and lateral) and average E/e' ratio. Notably, a reduction in diastolic function was observed in patients treated with doxorubicin alone or doxorubicin followed by trastuzumab but not in those treated with trastuzumab alone (42). Early changes in diastolic function are closely associated with a subsequent reduction of ejection fraction. Therefore, the evaluation of diastolic function appears to be helpful to evaluate the prognosis of cardiac function.

Speckle-tracking echocardiography (STE) has emerged as a highly sensitive technique for the detection of myocardial dysfunction, and the increasing maturity of STE has prompted the increased use of GLS as a technique for the assessment of cardiac function (44). GLS is a reliable, effective, repeatable and less load-dependent technique for measuring left ventricular longitudinal deformation, which is measured by STE, superior to LVEF, in the diagnosis and prognosis of acute heart failure and acute myocardial infarction (45,46). Several studies have evaluated GLS in the detection of CTRCD. Laufer-Perl *et al* (47) evaluated 291 consecutive patients with breast cancer who received different types of cancer therapy and divided them into two groups, according to whether GLS was reduced or preserved. Observation of the patients over a median follow-up period of 2.9 months indicated that reduced GLS had the potential to identify patients with an increased risk for the development of cardiac dysfunction. Notably, the incidence and mortality rates for the patients with reduced GLS were significantly higher than those of the patients with preserved GLS. A systematic review of studies on cardiotoxicity during and after cancer chemotherapy indicated that an early decline of 10-11% in GLS can be a strong predictor of subsequent cardiotoxicity (48). Sawaya *et al* (49) similarly found a reduction in GLS (<19%) in all patients who developed cardiac dysfunction; although the radial and circumferential components of the strain decreased over the duration of the

study, they were not predictive. Furthermore, a recent retrospective study by Santoro *et al* (50) highlighted the pivotal role of GLS in the prediction of cardiac outcomes after cancer therapy, suggesting that strain can be a parameter for guiding the initiation of cardioprotective strategies.

With improvements in the understanding of right ventricular (RV) function and measurement techniques, RV dysfunction secondary to chemotherapy has been identified as a factor that requires consideration. Evidence of impaired right-heart function first appeared in a single-case report by Bayer *et al* (51) in 2015. A 46-year-old patient with invasive ductal breast cancer developed right HF during treatment with trastuzumab after initial treatment with 5-fluorouracil + epirubicin + cyclophosphamide followed by docetaxel. The patient's heart function returned to normal after the discontinuation of the drug. Based on previous studies, it is speculated that the right heart is more sensitive to chemotherapy because its structure is thinner than that of the left heart and contains fewer myofibrils (52); therefore, its assessment may predict cardiac dysfunction that has not yet occurred in the left ventricle. For the measurement of right heart function, the guidelines from the British Society of Echocardiography are recommended; the main measurement indicators include RV ejection fraction, RV fractional area change, tricuspid annular plane systolic excursion, and RV longitudinal strain (53,54). However, further large scale studies are required to determine the significance of RV function monitoring in the prediction and prognosis of heart function in patients with breast cancer after treatment.

Biomarkers. Biomarkers accompanying myocardial injury identify patients at high risk of cardiotoxicity, and these patients often benefit from early treatment with, for example, angiotensin-converting enzyme inhibitors or b-blockers (31). It is expected that biomarkers may be able to predict future cardiotoxicity with high sensitivity. Cardiac troponins I and T (cTnI and cTnT) have been widely used as biomarkers of myocardial necrosis. Numerous retrospective studies have compared the concentrations of troponins before and after cancer treatment, especially in patients who developed cardiac events. In one study, an increase in cTnI following high-dose chemotherapy was found to be a strong predictor of poor cardiological outcome in patients with cancer (55). However, in another study, TnT, C-reactive protein and BNP did not change over a 2-year follow-up in patients with or without trastuzumab-mediated cardiotoxicity, while hs-cTnI proved to be a sensitive predictor of the development of cardiotoxicity (49). Therefore, hs-cTnI is a suitable biomarker for the screening of patients at high risk to determine whether more detailed tests are necessary. However, the high false-positive rate of hs-cTnI renders it unsuitable for diagnosis or for association with prognosis. In a study of 19 patients receiving chemotherapy with anthracyclines and trastuzumab, a significant increase in hs-cTnI was observed during the adjuvant trastuzumab therapy. In addition, the hs-cTNI level of patients whose left ventricular ejection fraction (≥) decreased by 5% was significantly higher compared with patients whose left ventricular ejection fraction (LVEF) decreased <5% (11.0±7.8 vs. 4.0±1.4 pg/ml; P<0.01) (56).

NT-proBNP is a hormone produced and released in response to ventricular wall stress, and has been identified as a biomarker for HF (57). Due to its value in the diagnosis of HF, a number of clinical trials have evaluated its use as a predictor of cardiotoxicity. A retrospective study of 71 patients with breast cancer who received anthracyclines demonstrated that a difference in the concentration of NT-proBNP between baseline and peak of >36% was able to predict left ventricular dysfunction (58). However, not all patients who developed cancer therapy-associated cardiotoxicity exhibited synchronous changes in NT-proBNP levels. Furthermore, no changes in NT-proBNP levels were observed in patients who received treatment only with trastuzumab regimens (41). According to currently available studies, it appears that only treatments containing anthracyclines induce changes in NT-proBNP (59-62). The levels of NT-proBNP may increase rapidly within 24 h of chemotherapy and then fall back to normal levels prior to the next cycle (63). Therefore, the detection of NT-proBNP 24 h after each cycle of chemotherapy is recommended.

Soluble suppression of tumorigenicity 2 (sST2) has been indicated to be a valuable biomarker associated with cardiac remodeling in patients with HF (64). Several studies have confirmed that sST2 exhibits a positive correlation with the E/e' ratio, an echocardiographic indicator of left ventricular systolic function, in patients with breast cancer receiving chemotherapy and also those undergoing adjunctive radiotherapy (65-67).

Other serum indicators have been shown to be valuable in the prediction of chemotherapeutic-associated cardiotoxicity. For example, high levels of placental growth factor and growth differentiation factor 15 were found to be associated with CTRCD in patients receiving trastuzumab therapy (61). In addition, myeloperoxidase exhibited a promising effect in the evaluation of the CTRCD risk of anthracyclines, both at baseline and throughout follow-up (68). Moreover, a study of the levels of certain microRNAs (miRNAs) in patients with breast cancer during and after anthracycline-containing chemotherapy revealed that the elevation of CHF-associated miRNAs, particularly miR-423-5p, was highly associated with the development of CTRCD (67). However, none of the aforementioned biomarkers have an appropriate balance of sensitivity and specificity, and more experiments are required to identify ideal biomarkers.

CMRI. CMRI is recommended when it is not possible to diagnose the cardiac condition with other tools or if the LVEF is on the borderline of normal (31). Compared with echocardiography, CMRI is more accurate and repeatable. It is especially suitable for the detection of diffuse myocardial fibrosis, but it is also limited by poor patient compliance (69,70). A study reviewed a cohort of adult survivors of childhood cancer who had been treated with chemotherapy, and high false-negative rates for an LVEF <50% were observed with echocardiography compared with CMRI (71). Based on these findings, comprehensive cardiac assessments should be considered for patients with an LVEF between 50 and 59% (71).

4. Conclusions

The emergence of targeted drugs and immunotherapy has had a major impact on cancer treatment, providing more options to eliminate the cardiotoxicity caused by chemotherapeutic drugs

such as anthracyclines. However, targeted drugs such as trastuzumab have also caused reversible damage to the heart. The main manifestation is cardiac dysfunction, but cardiac arrest and acute myocardial infarction may also occur. Further coordination between oncologists and cardiologists is required to achieve a balance between tumor treatment and cardiac safety. A baseline cardiac assessment is recommended for all patients prior to chemotherapy, and surveillance strategies should be considered for individuals at high risk according to the tumor treatment strategy and the patient's previous medical history.

Although a variety of anthracycline-free treatment regimens have been proposed and used, it must be noted that most patients with breast cancer receive anthracycline-based tumor treatments. Considering the possible consequences, it is important to raise awareness of cardiotoxicity, particularly when anthracyclines are used in combination with anti-HER2 targeted drugs.

Numerous issues remain to be resolved. For example, definitions are required for the following: The manifestations of complications associated with non-anthracycline treatments and their potential pathophysiological mechanisms; early intervention and preventive measures for tumor treatment-induced cardiotoxicity; monitoring strategies and biomarkers that are able to detect early toxic reactions; the appropriate time at which treatment should be restarted after cardiotoxicity and whether the treatment measures require adjustment; and how best to comprehensively treat patients with cancer. Cardio-oncology is a booming field that requires the cooperation of oncologists and cardiologists. The development of this discipline will improve the survival rate, quality of life and prognosis of patients.

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Competing interests

The authors declare that they have no competing interests.

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