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REVIEW

Adjuvant breast cancer treatments cardiotoxicity and modern methods of detection and prevention of cardiac complications

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Abstract

The most common cancer diagnosis in female population is breast cancer, which affects every year about 2.0 million women worldwide. In recent years, significant progress has been made in oncological therapy, in systemic treatment, and in radiotherapy of breast cancer. Unfortunately, the improvement in the effectiveness of oncological treatment and prolonging patients' life span is associated with more frequent occurrence of organ complications, which are side effects of this treatment. Current recommendations suggest a periodic monitoring of the cardiovascular system in course of oncological treatment. The monitoring includes the assessment of occurrence of risk factors for cardiovascular diseases in combination with the evaluation of the left ventricular systolic function using echocardiography and electrocardiography as well as with the analysis of the concentration of cardiac biomarkers. The aim of this review was critical assessment of the breast cancer therapy cardiotoxicity and the analysis of methods its detections. The new cardio-specific biomarkers in serum, the development of modern imaging techniques (Global Longitudinal Strain and Three-Dimensional Left Ventricular Ejection Fraction) and genotyping, and especially their combined use, may become a useful tool for identifying patients at risk of developing cardiotoxicity, who require further cardiovascular monitoring or cardioprotective therapy.

Keywords Cardiotoxicity; Heart failure; Breast cancer; Biomarkers; Oncological treatment

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Introduction

Epidemiology breast cancer

The most common cancer diagnosis in women is breast cancer, which affects about 2.0 million women worldwide every year between 45 and 69 years of age, and about half a million die because of it.[1] The most important factors increasing the risk of breast cancer include alcohol abuse, smoking (especially before the age of 44 years), genetic factors, a family history of cancer, high socioeconomic status, the use of hormone replacement therapy in postmenopausal women and also contraceptives, a history of benign breast lesions, more advanced age (over 50 years), and reproductive factors. Genetic factors particularly include gene mutations affecting BRCA1 (breast cancer susceptibility gene 1; breast cancer 1, early onset located on a long arm of chromosome 17) and BRCA2 (breast cancer susceptibility gene 2; breast cancer 2, early onset located on a long arm of chromosome 13). Reproductive factors embrace early puberty, late menopause, and late age of the first full-term pregnancy.[1,2] Owing to the introduction of population screening tests in 1986 in the UK and in the USA as well as in 2003 in the European Union member countries, the detection of breast cancer at an early stage of the disease development has increased. The related mortality has decreased. Currently, mammography is a screening

test recommended by European and American Cancer Societies; in Europe, mammography is intended for women aged 50–69 years to be performed every 2 years.[1–4]

Search strategy

We searched the electronic database PUBMED (2000 to 2020). Additionally, abstracts from national and international cardiovascular meetings, summaries of product characteristics, and selected monographs were searched. When necessary, the relevant authors were contacted to obtain further data. The main data search terms were breast cancer, adjuvant therapy, radiotherapy, toxicity of oncological treatment, diagnosis and cardiotoxicity, biomarker(s), marker(s), microRNA, anthracycline transporter proteins, and diagnosis and heart failure.

Pathomechanism and clinical symptoms of cardiovascular damage in patients undergoing chemotherapy and radiotherapy for breast cancer

The improvement in the effectiveness of oncological treatments and the prolongation patients' life expectancy are in some patients associated with the occurrence of organ complications as side effects of this treatment. The most common complications involve the dysfunction of the cardiovascular system manifested by damage of cardiomyocytes. Such damage can lead to asymptomatic left ventricular dysfunction or even overt heart failure, abnormal valve function, cardiac arrhythmias and conduction disorders, myocarditis, pericarditis, as well as endothelial damage and premature development of atherosclerosis and thromboembolic complications.[5–9]

Myocardial damage after the use of cardiotoxic drugs in women (chemotherapy-related cardiac dysfunction; CTRCD) is defined as a decrease in left ventricular ejection fraction (LVEF) of >10 percentage points, to a value $<53\%$.[10,11] Among oncological drugs with proven cardiotoxic effects, there are cytostatic agents (anthracycline antibiotics, 5-fluorouracil, and cyclophosphamide), molecularly targeted drugs (trastuzumab and pertuzumab), taxanes, and radiotherapy.[5,6,8,9]

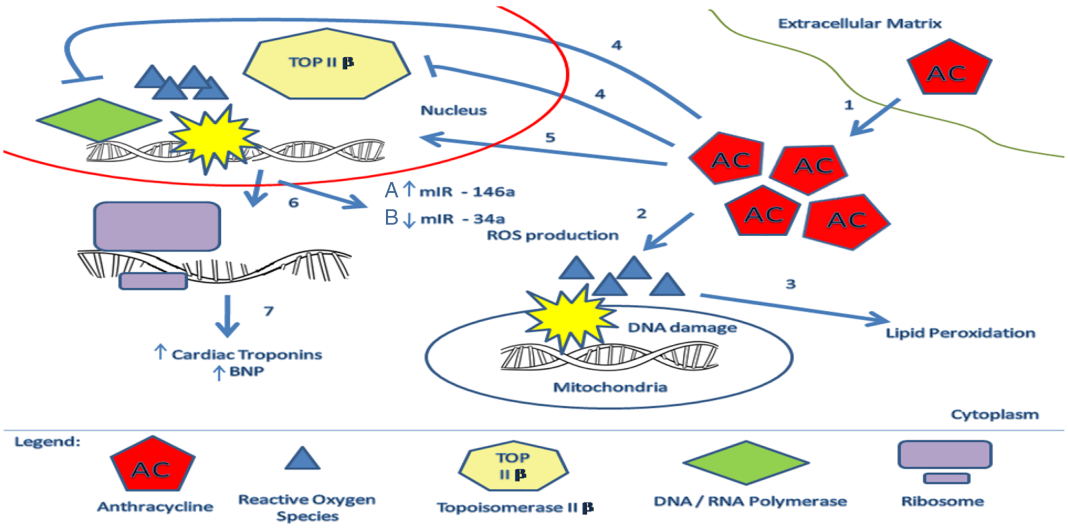
Anthracyclines

Anthracyclines are antibiotics produced by *Streptomyces peucetius var.caesius*, which are commonly used in the treatment of breast cancer.[12,13] Their cardiotoxic effects are related to several mechanisms like DNA structure damage, lipid peroxidation, and changes in the structure of cell membranes[12,13] as well as in the activation of p53 (tumour-suppressor protein), mitochondrial dysfunction, the generation of free oxygen radicals, and, in consequence, the death of myocardial cells.[14–16]

Another important mechanism for the cardiotoxicity of anthracycline drugs is associated with excessive accumulation of iron ions in cardiomyocytes and the production of free radicals.[17,18]

Apoptosis is another mechanisms of myocardial cell damage. Anthracyclines inhibit the phosphatidylinositol 3-kinase (PI3K/Akt) pathway,[19–22] altering cell susceptibility to anthracycline-induced apoptosis (*Figure* 1).[19–22]

Figure 1 Actions of anthracyclines in the cell. After entering the cell, anthracyclines (AC) cause mitochondrial damage and disrupt transcription in nuclear DNA.



Regardless of the mechanism, the action of anthracyclines finally causes the damage to genetic material and blocks cell proliferation, which consequently leads to the death of both cancer and myocardial cells.[12–22]

Anthracycline-induced cardiotoxicity can be divided into acute, early-onset chronic progressive cardiotoxicity, and late-onset chronic progressive cardiotoxicity.[23–26] Acute toxicity is quite rare (<1%), and it does not depend on the dose. It occurs during the infusion of cytostatics or up to 2 weeks after its completion. The most common clinical image of acute anthracycline-induced cardiotoxicity are the supraventricular arrhythmias, symptoms suggestive of myocarditis and pericarditis, left ventricular systolic dysfunction, and changes in the electrocardiogram (non-specific ST-T segment changes and QTc interval prolongation). The acute cardiotoxicity is usually reversible, but if it is accompanied by an increase in cardiac biochemical markers, it can lead to progressive heart failure.[23–25] Early-onset chronic progressive cardiotoxicity occurs in 1.6–2.1% of patients, and it often develops asymptomatically within the first 12 months after the completion of treatment. Late-onset chronic progressive cardiotoxicity occurs in 1.5–5% of patients after 1 year from the initial exposure and even after 10–20 years after the completion of anthracyclines treatment.[23–26] The anthracycline cardiotoxicity depends on a total cumulative dose. Currently, the maximum doxorubicin dose is 450–550 mg/m^2. The dose of 450 mg/m^2 is used in case of patients with concomitant risk factors for cardiomyopathy, while the dose of 550 mg/m^2 can be used in those without additional risk factors.[27] The use of doxorubicin at a dose exceeding the maximum dose significantly increases the risk of myocardial damage and left ventricular dysfunction.[27,28] This risk is around 5% for the 400 mg/m^2 dose, 26% for the 550 mg/m^2 dose, and over 48% for the total dose of 700 mg/m^2.[28] Anthracycline-induced cardiotoxicity is manifested by progressive and mostly irreversible impairment of diastolic function, followed by left ventricular systolic dysfunction, accompanied by cardiac arrhythmias, low electrocardiographic QRS voltage and an increase in cardiac troponin levels.[23–26] However, there is increasing evidence of myocardial recovery after anthracycline-induced damage. Cardinale *et al*., in the study of 201 patients with myocardial injury after anthracycline treatment (LVEF < 45%), observed normalization of the LVEF in 64% of the patients that treatment with enalapril and carvedilol within 2 months after the completion of chemotherapy.[29]

Targeted therapy for breast cancer

Recently, oncological treatment of breast cancer has been supplemented with targeted therapy involving drugs directed at specific molecular targets, such as membrane receptor kinases. The membrane receptor kinases are engaged in signalling pathways that are essential for the development of cancer. They include substances that act extracellularly (monoclonal antibodies) or intracellularly (tyrosine kinase inhibitors).[5,8,27] Monoclonal antibodies bind to specific receptors on cell surface, thus inhibiting signalling pathways regulated by these receptors. Antibodies and small molecule inhibitors of specific HER2 receptor kinases are main compounds used in targeted therapy of breast cancer.[5,8,27,28]

Monoclonal antibodies

Trastuzumab—human epidermal growth factor receptor type 2 (HER2) antagonist

Trastuzumab is the representative of the first group of drugs used in the therapy of breast cancer overexpressing HER2 receptors.[5,8,30] It is a humanized monoclonal antibody targeting the human epidermal growth factor HER2 receptor.[6,30–33] Trastuzumab-related myocardial dysfunction, especially in combination with anthracyclines, is a significant limitation of oncological therapy. HER2 receptor is expressed by myocardial cells. As a result of trastuzumab activity, oxidative stress increases the concentration of angiotensin II in cardiomyocytes, which blocks the binding of neuregulin 1 to HER receptors, inhibiting anti-apoptotic cell pathways. Blocking HER2-activated cell pathways impairs growth and repair mechanisms in cardiomyocytes, which results in myocardial dysfunction.[34,35] Myocardial damage is in most cases reversible. However, the evidence from retrospective studies indicates that the cardiotoxic side effects of trastuzumab may persist many years after the completion of the therapy; consequently, they are not always reversible as it was initially suggested.[34,36,37] Cardiotoxicity involves structural and functional changes in contractile proteins and mitochondria and rarely leads to cell death. Moreover, it does not depend on the drug dose. It develops during treatment or in a short period after the completion of chemotherapy. The most common clinical image of anti-HER2-related cardiotoxicity is left ventricular systolic dysfunction, without any associated changes in electrocardiographic records, with rarely co-existing severe symptoms of heart failure.[36–37]

Therapies based on the combined administration of anthracyclines and trastuzumab improve treatment results by over 50% and increase the survival rate of patients with HER2 positive breast cancer by 35%.[38–41] The effectiveness of the combined use of these drugs is unfortunately limited by an increased risk (5–10%) of myocardial dysfunction and severe heart failure.[39] Cardiomyocyte damage related to anthracycline activity increases HER2 expression, which activates intracellular repair processes.[39–41] Inhibition of HER2 activity by trastuzumab increases myocardial cell susceptibility to anthracycline toxicity.[39–41] Myocardial injury following the combination therapy of anthracyclines and trastuzumab is usually irreversible.[41]

Bevacizumab—VEGF endothelial growth factor antagonist

Despite the breast cancer indication for bevacizumab had been withdrawn by FDA after concluding that the drug has not been shown to be safe and effective for the treatment of breast cancer,[42,43] some experts consider it an option for extensive cutaneous inflammatory disease due to its potential antiangiogenic effect.[43]

Tyrosine kinase inhibitors

Lapatinib is an oral, reversible inhibitor of EGFR and HER2 tyrosine kinases approved for the treatment of patients with HER2-positive metastatic breast cancer who fail to respond to anthracyclines, taxanes, and trastuzumab therapy.[5,7,44,45] Cardiotoxicity induced by tyrosine kinase inhibitors develops when the target of an inhibitor is a kinase whose function is important for the proper functioning of the cardiovascular system.[28]

Lapatinib treatment is associated with a lower risk of cardiovascular adverse reactions than trastuzumab.[46,47] Lapatinib-related cardiotoxicity in the form of reversible left ventricular systolic dysfunction develops in approximately 1.5% of patients. However, it is not a reason for a permanent discontinuation of oncological treatment.[48]

Alkylating agents—cyclophosphamide

Apart from anthracycline drugs, in a conventional chemotherapy for breast cancer, alkylating agents such as cyclophosphamide are also used.[5,8,49] The pathogenesis of cyclophosphamide-related cardiotoxicity is associated with toxic effects of its active metabolites on cardiomyocytes and endothelial cells, through the production of free oxygen radicals and lipid peroxidation.[50] In consequence, this leads to vascular endothelial damage, exudate, haemorrhage, and interstitial oedema, which clinically manifest as haemorrhagic myocarditis, myocarditis, and pericarditis with accompanying pericardial fluid and asymptomatic left ventricular dysfunction or symptomatic heart failure that is usually reversible.[51–53] Moreover, changes in electrocardiographic record, including supraventricular and ventricular tachyarrhythmias, atrioventricular conduction blocks, low amplitude of QRS complexes, and changes in the ST-T segment are observed.[20,54] Symptoms of myocardial damage occur up to 10 days after drug administration, and usually, they disappear after few days. One of the most important risk factor for cyclophosphamide-induced cardiotoxicity is the use of high drug doses (Santos *et al*. more than 270 mg/kg over 1–4 days and Goldberg *et al*. doses equal or greater than 1.55 g/m^2).[55,56] However, acute toxicity has been reported even after total doses of 100 mg/kg.[53] Furthermore, it seems that cyclophosphamide cardiotoxicity manifests more often in lymphoma patients than breast cancer patients (Brockstein *et al*.).[57] The advanced age, pre-existing heart disease, concomitant or previous use of cardiotoxic drugs, and the history of local radiation of the heart region are also associated with cyclophosphamide-related cardiotoxicity.[55–57]

Antimetabolites

Antimetabolites, fluoro-derivatives of pyrimidine, such as 5-fluorouracil (5-FU) and its oral prodrug, capecitabine, are compounds that cytostatic activity is related to the inhibition of the production of nucleic acid precursors necessary for DNA replication.[58–61] The pathomechanism of fluoropyrimidine-related cardiotoxicity is associated with the toxic effects of their metabolites, that is, fluoroacetate and fluoro-β-alanine, on coronary artery myocytes and direct damage to cardiomyocytes.[62,63] Resting and exercise angina as well as myocardial infarction resulting from coronary vasospasm and reduced myocardial perfusion are the most common clinical images of fluoropyrimidine-related cardiotoxicity.[64–68] Moreover, supraventricular[69] and ventricular tachyarrhythmias,[70] bradycardia,[71] myocarditis and pericarditis,[72,73] heart failure,[74] and even deaths.[75–77]

Microtubule inhibitors

Substances belonging to microtubule inhibitors used in oncological therapy of breast cancer include taxanes: paclitaxel, isolated from short-leaf yew (*Taxusbrevifolia*) and docetaxel, isolated from English yew (*Taxusbaccata*).[5,8,78] Taxanes in combination with anthracyclines exert the strongest toxic effect on the heart muscle.[79–82] Taxanes stimulate the transformation of an anthracycline molecule into its alcohol derivative in a NADPH reductase-dependent manner, thus resulting in the formation of doxorubicinol and epirubicinol, which impair iron and calcium homeostasis and increase the production of oxygen free radicals more intensively than doxorubicin and epirubicin.[83] Symptoms of taxane-induced cardiotoxicity include left ventricular dysfunction, asymptomatic bradycardia, arrhythmias, and conduction disorders.[84,85]

Ionizing radiation

Apart from systemic treatment, radiation therapy plays a very important role in adjuvant therapy for breast cancer.[5,8,86] Due to the widespread use of this method of treatment, adverse effects of radiation therapy on the cardiovascular system are more often observed, even many years after irradiation.[87–90]

The pathomechanism of the damaging effect of radiation therapy on cardiovascular system structures involves direct ionization and damage of cell components by radiation and by water radiolysis products.[91] The coronary and

microcirculation damage is one of radiotherapy complication. It can lead to faster development of coronary heart disease, complicated by atherosclerotic plaque rupture, thrombosis, and frequently asymptomatic myocardial infarction as a result of radiation-related nerve ending damage.[87] In case of radiation due to left breast cancer, the left anterior descending artery of the left coronary artery is most often affected, and stenoses are usually located in the ostial part of the vessel.[92] Significant lesions in coronary vessels occur 10–15 years after radiotherapy.[93]

Valve defects are another significant complication after ionizing radiation treatment for breast cancer, which occurs in about 10% of patients.[90] This defect mainly affects the valves of the left part of the heart, and pathological changes include fibrosis and calcification of the aortic bulb, aortic valve leaflets, mitral ring, and a basal and a central part of the mitral valve leaflets.[94–96] This most often leads to mitral and aortic valve regurgitation and also to aortic stenosis.[94–96] Mean time to onset of clinical symptoms of radiation-induced valve injury is approximately 98 months.[94]

Heart failure is a complication, which is also observed after the use of ionizing radiation.[90] Radiation induces the formation of interstitial fibrosis loci with varying diameters in the myocardium. These loci are frequently located on the anterior wall of the heart, and they rarely cover the entire muscle.[90,97] It can also cause microcirculation damage by creating inflammatory infiltrates within small-sized and medium-sized arteries, fibrosis, and endothelial cell damage.[88,90] HFrEF is more frequently observed in patients who received both anthracycline and radiation therapy.[90]

Currently, the incidence of this complication is decreasing due to the introduction of modern radiotherapy techniques based on a computerized treatment planning system (TPS).[98–99] Acute radiation-induced pericarditis occurs after 2 to 145 months (mean 58 months) after radiotherapy in 2–5% of patients.[100,101] Late radiation-induced pericardial disease develops between 6 months to 15 years after radiation therapy, on average, after 12 months.[92,102,103] It can occur in the form of acute late pericarditis or the presence of chronic fluid in the pericardial sac, which is often asymptomatic.[23] In most of cases, it resolves spontaneously; however, in up to 20% of patients, especially those who received high doses of radiation, the development of chronic and/or constrictive pericarditis has been reported.[23,102] The damage to the cardiac conduction system and heart autonomic system is a very rare but equally important complication of radiation therapy. It occurs especially after the administration of high doses of radiation, including high fractional doses.[23,103] The clinical picture involves mainly sinus bradycardia, conduction blocks at all levels of the conduction system, and sick sinus syndrome.[23,90] Also, QTc prolongation has been observed in patients receiving combination therapy with anthracyclines. Autonomic system damage is manifested by inadequate sinus tachycardia and a lack of heart rate variability.[23,91,103]

Toxic effects of radiation therapy on the heart muscle are mainly determined by the dose, the location of the tumour, and the volume of the heart exposed to radiation (the risk increases significantly when the volume of the heart irradiated exceeds 50%).[90]

The summary of cardiotoxic symptoms related to adjuvant breast cancer treatment as well as prevention methods is presented in *Table 1*.[8,11,23–26,36,39,40,41,46,48,51,56–57,60,62–77,84,82,85–90,92–99,102–132]

Predictors of myocardial damage after chemotherapy and radiation therapy for breast cancer

Adjuvant therapy for breast cancer (both systemic and radiation therapy) is necessary to reduce morbidity and mortality.[5,8] The cardiotoxicity of this therapy can lead to the development of heart failure and may negatively affect quality of life and prognosis.[11,23,24] The high cardiotoxicity-related morbidity and mortality rates associated with antineoplastic therapy for breast cancer could be reduced with the early use of cardioprotective drugs.[23,24,121–131]

Therefore, it is important to assess the cardiovascular system in each patient before starting oncological therapy and to closely monitor heart muscle during and after treatment.[23,24,132–133] The choice of myocardial function assessment method and the time at which it should be performed in patients with planned adjuvant treatment of breast cancer are precisely specified in the recommendations of American (ASCO, ASE, the American Society of Echocardiography) and European (ESMO, European Society for Medical Oncology; ESC, European Society of Cardiology; EACVI, the European Association of Cardiovascular Imaging) experts in oncology and cardiology.[11,23,24,133] Echocardiography is the first-line diagnostic tool for the assessment of the cardiovascular system in patients undergoing therapy for breast cancer, which is recommended by the aforementioned experts.[11,23,24,133] The ESC, ESMO, and ASE/ECACVI guidelines also recommend the measurement of cardiac biomarkers together with echocardiography after each chemotherapy cycle (ESC;ESMO)[23,24] or during follow-up echocardiography (ASE/ECACVI).[11]

The most important current recommendations are summarized in *Table 2*.[11,23,24,133–135]

The detection of myocardial damage at the subclinical stage enables early initiation of cardioprotective therapy and prevents the development of irreversible heart failure.[23,24,133] Diagnostic methods, both imaging and biochemical, which are recommended and currently used in the monitoring of patients with breast cancer who receive potentially cardiotoxic chemotherapy, are an important tool in the prevention of heart failure.[11,23,24,133–135] However, the low sensitivity of left ventricular ejection fraction

Table 1 Cardiotoxicity of adjuvant breast cancer treatment and prevention methods[8,11,2 3–26,36,39,40,41,46,48,51,56–57,60,62–77,84,82,85–90,92–99,102–132]

Adjuvant agents	Cardiovascular adverse effects	Prevention
Anthracycline (e.g. doxorubicin and epirubicin)	Left ventricular dysfunction, heart failure, myocarditis, pericarditis, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and QTc prolongation (doxorubicin)	• Identification and treatment of cardiovascular risk factors • Limiting of cumulative dose • Alternative delivery systems (liposomal doxorubicin) • Continuous infusions • The use of cardioprotective drugs: Dexrazoxane, ACE-Is or ARBs, beta-blockers, statins • Avoiding of QT prolonging drugs and the management of electrolyte abnormalities • Aerobic exercise
HER-2-directed therapies (e.g. trastuzumab and pertuzumab)	Left ventricular dysfunction and heart failure	• Identification and treatment of cardiovascular risk factors • The use of ACE-Is, beta-blockers
Alkylating agents (e.g. cyclophosphamide)	Left ventricular dysfunction, heart failure, myocarditis, pericarditis, arterial thrombosis, bradycardia, atrial fibrillation, and supraventricular tachycardia	• Identification and treatment of cardiovascular risk factors • Treatment of comorbidities (CAD, HF, PAD, and HTN)
Antimetabolites (e.g. 5-fluorouracil and capecitabine)	Coronary thrombosis, coronary artery spasm, heart failure, left ventricular dysfunction, Tako-Tsubo-like syndrome, cardiomyopathy, myocarditis, pericarditis, and arrhythmias	• Identification and treatment of cardiovascular risk factors • Treatment of comorbidities (CAD, HF, PAD, and HTN)
Taxanes (e.g. paclitaxel)	Left ventricular dysfunction, ventricular ectopy, and bradycardia, and heart block	• Identification and treatment of cardiovascular risk factors • Treatment of comorbidities (CAD, HF, PAD, and HTN)
Tyrosine kinase inhibitor	Left ventricular dysfunction and QTc prolongation	• Identification and treatment of cardiovascular risk factors • Treatment of comorbidities (CAD, HF, PAD, and HTN) • Avoiding of QT prolonging drugs • Management and treatment of electrolyte abnormalities
Radiation therapy	Coronary artery disease, cardiomyopathy, valvular disease, pericardial disease, and arrhythmias	• Minimizing of cardiac radiation: lowering the dose of radiation and reducing cardiac volume exposed • Use of modern techniques based on 3D treatment planning with a dose–volume histogram and virtual simulation programme

ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; HF, heart failure; HTN, hypertension; PAD, peripheral artery disease.

assessment limits its use in preventive strategy.[136,137] New parameters, such as biomarkers and new imaging parameters, might be used in the early detection of myocardial dysfunction.

Imaging tests

Echocardiography

Besides electrocardiography (including measurement of heartrate QTc), also echocardiography is the primary diagnostic test for chemotherapy-related myocardial damage (CTRCD).[11,23,24,133–135] It is the most commonly used tool for the assessment of cardiac function before the qualification for chemotherapy, as well as during treatment, due to its widespread availability, low cost, and safety.[11,23,24,133–135]

Left ventricular ejection fraction (LVEF), estimated using the 2D biplane Simpson's method or more precisely, with the use of three-dimensional (3D) technique, is the basic parameter assessed during this examination.[11,23,136,137] According to the ASE/EACVI consensus, the decrease of LVEF by 10% to a value below 53% is considered as the evidence of an existing CTRCD.[11]

The decrease in left ventricular ejection fraction is a late, often irreversible sign of toxic damage to myocardium.[132] The assessment of global longitudinal strain (GLS) is a sensitive echocardiographic method for the detection of early myocardial damage.[138–142] Myocardial deformation is measured using tissue Doppler mode or the speckle tracking echocardiography (STE). They evaluate both segmental and generalized disorders of systolic and diastolic functions of

Table 2 Diagnostic procedures for early detection of chemotherapy-induced breast cancer cardiotoxicity according to FDA, ASE/EACVI, ASCO, ESC, ESMO recommendations[11,23,24,133–135]

		Measurement of LVEF by echocardiography		
Guidelines	Chemotherapy agents	Baseline	During treatment	At the completion of therapy
FDA[134,135]	Anthracycline therapy	+	For higher cumulative anthracycline doses	Not specified
	HER2 targeted therapy (trastuzumab)	+	Every 3 months	Every 6 months for at least 2 years following the completion of trastuzumab as a component of adjuvant therapy
ASE/ EACVI[11]	Anthracycline therapy	+	If the dose is >240 mg/m^2 examination should be performed prior to each additional 50 mg/m^2 (LVEF and GLS with troponin I)	At the completion of therapy and 6 months later (LVEF and GLS with troponin I)
	HER2 targeted therapy	+	Every 3 months (LVEF and GLS with troponin I)	No routine examination recommended if asymptomatic
	HER2 targeted therapy after anthracycline treatment	+	Every 3 months (LVEF and GLS with troponin I)	6 months later (LVEF and GLS with troponin I)
ASCO[133]	- AC (e.g. doxorubicin >250 mg/m^2); RT (≥30 Gy in case of the heart being in the treatment field) - Low dose AC (<250 mg/m^2) + low dose RT (<30 Gy) - AC + Trast - Low dose AC or trast + risk factors[a]	+	Frequency should be determined by health care providers on the basis of clinical judgement and patient circumstances	Evaluation may be considered 6 to 12 months after the completion of a treatment in patients at increased risk
ESC[23]	Anthracyclines therapy	+	If the dose exceeds 240 mg/m^2 in patients with high baseline risk	At the completion of therapy
	HER2 targeted therapy	No routine recommended	Every 3 months	At the completion of therapy
	HER2 targeted therapy after anthracyclines treatment	+	Every 3 months	At the completion of therapy
ESMO[24]	Anthracyclines therapy	+ With cardiac biomarkers[b,c] [IIIA]	After a cumulative dose of doxorubicin 250 mg/m^2 After each additional 100 mg/m^2 (LVEF and GLS) [IA] With cardiac biomarkers[b] every 3–6 weeks or before each cycle [IIIC]	At 6–12 months, 2 years post-treatment Periodically thereafter cardiac biomarkers[b] [IIIB]
	HER2 targeted therapy	+	Every 3 months (LVEF and GLS) [IIB] With cardiac biomarkers[b] [IIIC]	At 6–12 months, 2 years post-treatment Periodically thereafter cardiac biomarkers[b] [IIIB]

AC, anthracycline; ASCO, American Society of Clinical Oncology; ASE, American Society of Echocardiography; BNP, brain natriuretic peptide; EACVI, the European Association of Cardiovascular Imaging; ESC, European Society of Cardiology; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor type 2; NT-proBNP, N-terminal pro brain natriuretic peptide; RT, radiation therapy; trast, trastusumab.

[a]Risk factors included age ≥60, compromised cardiac function (e.g. history of myocardial infarction, moderate valvular disease, and borderline LVEF) or ≥2 cardiovascular risk factors (smoking, hypertension, diabetes mellitus, and hyperlipidaemia).[136]

[b]Cardiac biomarkers: TroponinT/I and BNP/NT-proBNP.[24]

[c]For high risk patients (with pre-existing significant CVD) and those receiving high doses of cardiotoxic chemotherapy such as anthracycline, baseline measurement of such cardiac biomarkers should be considered [III, A].[24]

both ventricles.[138–142] The measurement of myocardial deformation, especially with the use of STE method, is characterized by high repeatability of measurements and precedes the decrease in left ventricular ejection fraction during oncological treatment.[138–142] The ASE/EACVI consensus defines that a relative percentage decrease of GLS by >15% from baseline is a clinically relevant evidence of subclinical left ventricular dysfunction.[11] The disadvantage of this method involves the variability of results depending on the device, software, or patient's age and sex.[11] Therefore, it is recommended to evaluate GLS, preferably on the same device, by the same examiner, before the initiation of treatment, during and after the completion of treatment; subsequent measurements should be compared with baseline measurements.[11,23]

Echocardiography can also be used to assess other parameters of myocardial function, which have not been included in current recommendations and which may be important in predicting the subclinical cardiotoxicity of radiotherapy and chemotherapy.[143–148]

Changes in left ventricular diastolic function parameters, including mitral inflow wave velocity, E/A ratio, pulmonary vein flow, isovolumetric diastolic time, or tissue Doppler velocity, can be observed in patients undergoing oncological treatment a few hours after chemotherapy.[143]

A significant decrease in right ventricular systolic and diastolic function and changes in the volume and function of the left atrium in treated oncological patients are also considered as an early marker of CTRCD.[143,145,146,148]

Studies and results presenting promising parameters of significant importance in the assessment of oncological treatment related complications are summarized in *Table 3*.[136–148]

Other imaging techniques

Radioisotope ventriculography (MUGA, multiple gate acquisition scan) eliminates inter-observer variation in LVEF assessment. However, it exposes patients to radiation and provides limited information on cardiac structure and diastolic function. In turn, magnetic resonance imaging of the heart allow to thoroughly estimate myocardial structures and function, which are difficult to evaluate by echocardiography, particularly in case of unsatisfactory quality of echocardiographic imaging.[11,149] Moreover, it is the non-invasive tool for assessment and monitoring of cardiotoxicity, including cardiac tissue characterization, perfusion, and features, which may assist the differential diagnosis (ischaemic and non-ischaemic) and management of myocardial injury in cancer survivors.[149] However, due to the high cost and limited availability, this imaging method is not the first-line examination used in routine monitoring of patients undergoing cardiotoxic therapy.[23]

Biomarkers

The monitoring of myocardial function with the use of repeated echocardiographic examinations in order to detect toxic effects of adjuvant breast cancer therapy on myocardium is still a suboptimal approach.[11] The determination of cardiomyocyte-specific plasma biomarkers has proved to be a promising complement to routine echocardiography.[150] Plasma biomarkers, cardiac troponins and natriuretic peptides, have been evaluated in many studies for their usefulness for early detection of myocardial damage in patients without clinical symptoms.[151–159] Troponin concentration shows high specificity and sensitivity for myocardial damage detection. Its measurement is minimally invasive, cheaper than imaging tests, standardized (there is no variability between observers), and shows high negative predictive value, and the result is independent of the mechanism of cardiotoxicity.[24,160–161] Cardinale *et al*. proved the superior diagnostic value of cardiac troponins in patients receiving high-dose (>240 mg/m^2) anthracycline chemotherapy than low-dose anthracycline therapy.[162] The troponin levels closely correlate with the subsequent reduction of LVEF[161]; therefore, it allows identification of patients who will require further cardiovascular monitoring or cardioprotective therapy.[24,152–154]

In turn, the study of Rüger *et al*. revealed that N-terminal-pro-brain natriuretic peptide (NT-proBNP) and haemoglobin but not cardiac troponin T are strongly associated with cardiotoxic reactions. In this study, electrocardiogram, echocardiographic, and haemodynamic parameters as well as NT-proBNP and cardiac troponin T were assessed in 853 early-stage breast cancer women to establish predictors of cardiotoxic reactions while undergoing chemotherapy.[163] Natriuretic peptides, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and their N-terminal fragments (NT-proANP, N-terminal-pro-atrial natriuretic peptide; NT-proBNP) are released by cardiomyocytes in response to volume or pressure overload and wall stretching. It results in increased glomerular filtration and the excretion of water and sodium, as well as the inhibition the activity of renin-angiotensin-aldosterone (RAA) system. Moreover, they inhibit the sympathetic nervous system and directly dilate blood vessels.[159] Therefore, they are involved in the maintenance of homeostasis related to blood pressure and circulating blood volume. Plasma level of natriuretic peptide is an important prognostic indicator of 30 day mortality in patients with decompensated heart failure related to ischaemic and non-ischaemic causes.[164,165] Moreover, in combination with cardiac troponins, they are also biomarkers of chronic and functional heart damage.[166,167] Therefore, their measurement is recommended and commonly used in the diagnosis and monitoring of heart failure treatment (mainly BNP and NT-proBNP due to their longest half-life).[168] In the largest study on the role of BNP in the detection of early

Table 3 Echocardiographic markers of early detection of chemotherapy-induced cardiotoxicity in breast cancer[136–148]

Echocardiographic parameters	Study	Results	Conclusions
Left ventricular ejection fraction assessed using three-dimensional (3D) echocardiography	Thavendiranathan *et al.*[136]	Significantly decreased: Non-contrast 3D-EF, end-diastolic, and end-systolic volume 3D-EF is also characterized by the best intra-observer and inter-observer as well as test–retest variability	Non-contrast 3D-EF was the most reproducible technique for LVEF and LV volume measurement within more than 1 year of follow-up
	Walker *et al.*[137]	A strong correlation with CMR: LVEDV in RT3D TTE (r = 0.87 at baseline; r = 0.95 at 12 months, respectively) LVEF in RT3D TTE (r = 0.91 at baseline; r = 0.90 at 12 months, respectively) A modest correlation with CMR: LVEDV in 2D TTE (r = 0.64 at baseline; r = 0.69 at 12 months, respectively) LVEF in 2D TTE (r = 0.31 at baseline, r = 0.42 at 12 months, respectively)	RT3D TTE is an accurate, and reproducible alternative imaging modality for the serial monitoring of LVEF in patients with breast cancer
Two-dimensional speckle tracking echocardiography strain imaging of the left ventricle (2D-STE)	Lo *et al.*[138]	Global and segmental systolic strain parameters (regional strain and strain rate) with the largest decrement in the apical segment (segments with the highest radiation dose exposure) Significantly decreased (at 6 weeks after RT in comparison with baseline): Apical peak systolic strain of −21.21% ± 3.49% before RT vs. −18.69% ± 3.34% after RT, percentage change of 11.88%, P = 0.002; Apical peak systolic SR of −1.17 ± 0.24 s before RT vs. −1.04 ± 0.19 s after RT, percentage change of 11.11%, P = 0.008) Early diastolic SR in the apical segments (apical early diastolic SR, 1.54 ± 0.45 s before RT vs. 1.35 ± 0.33 s after RT; percentage change of 12.34%; P = 0.034)	Global and segmental systolic strain parameters (regional strain and strain rate) may have a potential role in the evaluation of irradiation-related cardiotoxicity
	Luo *et al*[139]	Total GLS and GLS were significantly decreased of the endocardium in every view in group treated epirubicin at ≥360 mg/m^2; $P < 0.05$) compared with patient treated this drug in lower dose	Left ventricular longitudinal systolic dysfunction of the endocardium was detected during an early assessment using layer-specific 2DSTE
	Wang *et al.*[140]	Significantly decreased (before, during, and after chemotherapy): The GLS during (−16.5 ± 1.9)% and after (−16.0 ± 1.6)%, chemotherapy was significantly decreased ($P < 0.01$) compared with this before (−18.5 ± 1.7)% chemotherapy The GCS during (−19.3 ± 3.5)% and after (−19.2 ± 3.2)% chemotherapy was significantly decreased ($P < 0.01$) compared with this before (−20.9 ± 2.9)% chemotherapy The RS during (35.3 ± 5.2)% and after (35.0 ± 6.2)%, chemotherapy was significantly decreased ($P < 0.01$) compared with this before (39.2 ± 6.4)%, chemotherapy	GLS assessed in 2D-STE combined with hs-cTnT can effectively and precisely detect early symptoms of anthracycline-induced cardiotoxicity

(*Continues*)

Table 3 (continued)

Echocardiographic parameters	Study	Results	Conclusions
		No significant differences (before, during, and after chemotherapy): The LVEF: (63.8 ± 2.6%), (63.8 ± 2.8%), and (64.0 ± 3.3%), respectively ($P = 0.91$) T (GLS-SD), T (GCS-SD), and T (RS-SD) ($P > 0.05$ in all cases) There were no significant differences in LVEF, T (GLS-SD), T (GCS-SD), and T (RS-SD) before, during, and after chemotherapy The reduction of GLS was positively associated with the increase in hs-cTnT after chemotherapy ($r = 0.60$, $P < 0.01$)	
	Laufer-Perl *et al.*[141]	Significant predictors: In 64 consecutive patients, 12 (19%) had ≥10% GLS relative reduction, of which 75% had no concomitant ejection fraction reduction	GLS reduction is frequent in patients with active cancer, it precedes LVEF reduction and cannot be anticipated by other echocardiographic parameters
	Arciniegas Calle *et al.*[142]	Significantly reduced (compared with baseline): LV longitudinal strain, LV circumferential strain, circumferential peak systolic SR, circumferential peak early diastolic SR, right ventricular longitudinal strain, longitudinal peak systolic SR ($P < 0.05$) GLS at T1 (first cycle): the strongest indicator of subsequent cardiotoxicity [area under the curve: 0.85; cut-off value: 14.06; sensitivity: 91%; specificity: 83%; $P = 0.003$ (T0)]	Early changes in GLS are good predictors of subsequent development of anthracycline-trastuzumab-induced cardiotoxicity
Left ventricular diastolic dysfunction	Yaylali *et al.*[143]	Significantly increased (after anthracycline therapy): LA active emptying volume and fraction ($P = 0.0001$ and $P = 0.0001$); Mitral A velocity (0.8 ± 0.2 vs. 0.6 ± 0.2, $P = 0.0001$); Mitral E-wave deceleration time (201.2 ± 35.6 vs. 163.7 ± 21.8, $P = 0.0001$; Mitral Am (0.11 ± 0.02 vs. 0.09 ± 0.02, $P = 0.0001$); Mitral E/Em ratio (8.8 ± 3.2 vs. 7.6 ± 2.6, $P = 0.017$); Significantly decreased (after anthracycline therapy): LA passive emptying volume and fraction ($P = 0.0001$ and $P = 0.0001$); Mitral E/A ratio (1.0 ± 0.3 vs. 1.3 ± 0.3, $P = 0.0001$); Mitral Em (0.09 ± 0.03 vs. 0.11 ± 0.03, $P = 0.001$);	Impaired left ventricular diastolic function could contribute to the development of atrial arrhythmias in patients with breast cancer who underwent anthracycline therapy
Left ventricular regional wall motion abnormality	Barros *et al.*[144]	Regional wall motion abnormality 6.25 OR [1.03; 37.95; 95% CI]; $P = 0.046$	The assessment of segmental wall motion might be a useful tool in the early detection of myocardial dysfunction
Right ventricle dysfunction	AbdarEsfahani *et al.*[145]	Significantly increased: RV end-diastolic diameters and Tei index (0.31 to 0.37) ($P < 0.001$) Systolic pulmonary arterial pressure (20.63 to 22.24 mmHg, $P = 0.04$) Significantly decreased:	Significant decrease in RV systolic and diastolic function during chemotherapy can probably be considered as an early indicator of anthracycline-induced cardiotoxicity

(*Continues*)

Table 3 (continued)

Echocardiographic parameters	Study	Results	Conclusions
		RVFAC (49.83% to 43.59%), TAPSE (18.8 to 17.7 mm) ($P < 0.001$), E (57.06 to 46.59 cm/s, $P < 0.001$), E/A ratio (1.42 to 1.18, $P < 0.001$), E′ (16.73 to 12.4 cm/s, $P < 0.001$), E′/A′ ratio (1.21 to 0.9, $P < 0.001$), S′ (12.59 to 10.57 cm/s, $P < 0.001$)	
	Wang *et al.*[146]	Significantly decreased (in comparison with state before chemotherapy): RV GLS at C2 ($P < 0.05$), RV GLS and RV GAS at C4 and at C6 ($P < 0.05$) RV GLS and RV GAS correlate with FAC ($r = 0.37, 0.26$), TAPSE ($r = 0.43, 0.51$), and S′ ($r = 0.21, 0.36$) ($P < 0.01$) (a high sensitivity and specificity for identifying RV-FAC decline by >5%) RV GLS and RV GAS and significantly increased hs-cTnI level correlate with abnormal myocardial perfusion in ^{18}F-FDG imaging ($P < 0.05$) RV GLS < 18.2% enabled the diagnosis of RV impairment with a sensitivity of 92.9%, diagnostic specificity of 88.2% and an area under the curve of 0.87 RV GAS <26.8% enabled the diagnosis of RV damage with a sensitivity of 94.8%, a specificity of 86.6% and area under the curve of 0.86	Strain parameters based on three -dimensional speckle tracking echocardiography (3D-STI) can be considered as an early predictor of changes in the mechanical properties of the RVM related to chemotherapy with pirarubicin in breast cancer patients
Prolonged electromechanical delay	Choe *et al.*[147]	ΔLVEMDi: 23 ms was the optimal cut-off value for TIC prediction (sensitivity: 0.85; specificity: 0.78; area under the curve [AUC]: 0.882) ΔLVEMDp: 21 ms was the optimal cut-off value for TIC prediction (sensitivity: 0.96; specificity: 0.68; AUC: 0.860)	ΔLVEMDi and ΔLVEMDp may serve as predictors of subclinical cardiac dysfunction in breast cancer patients receiving trastuzumab
Atrial function	Bergamini *et al.*[148]	LAVI: an independent predictor of TZ-induced LV dysfunction in: • a clinical model, including age and hypertension (odds ratio per 5 mL/m^2 LAVI increase: 1.34, 95% confidence interval: 1.03–1.82, $P = 0.03$); • a haemodynamic model, including ventricular sizes and systolic blood pressure level (odds ratio per 5 mL/m^2 LAVI increase: 1.34, 95% confidence interval: 1.01–1.81, $P = 0.04$)	The predicted probability of developing cardiotoxicity increased progressively, in parallel with LAVI values
	Yaylali *et al.*[143]	Significantly prolonged (after anthracycline therapy): Left intra-atrial EMD (11.4 ± 6.0 vs. 8.1 ± 4.9, $P = 0.008$); Left inter-atrial EMD (19.7 ± 7.4 vs. 14.7 ± 6.5, $P = 0.001$);	Left atrial electrical conduction could contribute to the development of atrial arrhythmias in patients with breast cancer after anthracycline therapy

CMR, cardiovascular magnetic resonance imaging; EMD, electromechanical delay; GCS, global circumferential strain; GLS, global longitudinal strain; LAVI, left atrial volume index; LV, left ventricle; RT, radiotherapy; RT3D TTE, real time three-dimensional transthoracic echocardiography; RV, right ventricle; RV-FAC, right ventricle fractional area change; SR, strain rate; TAPSE, tricuspid annular plane systolic excursion; ΔLVEMDi, changes in the time intervals from QRS onset on electrocardiography to the beginning of transaortic flow on pulsed-wave Doppler echocardiography; ΔLVEMDp, changes in the time intervals from QRS onset on electrocardiography to the peak of transaortic flow on pulsed-wave Doppler echocardiography.

cardiotoxicity, Skovgaard *et al*.[156] demonstrated that in a group of 333 patients with different types of cancers, undergoing potentially cardiotoxic treatment, BNP level >100 pg/mL was a marker of early heart failure (HR: 5.5; 95% CI: 1.8 to 17.2, P = 0.003). The usefulness of BNP measurement in predicting early cardiotoxicity has also been demonstrated in meta-analysis of eight cohort studies performed by Ya-di Wang *et al*.[153] The study on the role of NT-proBNP as an early marker of cardiac dysfunction after the use of high doses of chemotherapy in patients with aggressive tumours revealed that persistent elevation of plasma NT-proBNP levels was associated with the deterioration of diastolic and systolic parameters of LV function as IRT (90 ms vs. 141 ms; $P < 0.0001$), DecT (162 vs. 224 ms; P = 0.0004), and LVEF (62.8% vs, 45.6%, $P < 0.0001$).[158] However, the interpretation of cardiac troponin and natriuretic peptide levels with reference to oncological therapy-induced cardiotoxicity has some limitations. The significant limitations of those methods are the lack of final agreement regarding the cut-off values for these parameters and their levels variability depending on the presence of concomitant diseases. Moreover, increased levels of cardiac biomarkers confirm pre-existing damage to the heart muscle cell.[159] Currently, ESC[23] and ASE/EACVI[11] experts recommend the determination of cardiac troponin as a supplement to the LVEF assessment during routine monitoring of patients undergoing cardiotoxic therapy.[11,23]

New plasma biomarkers

Many studies evaluated the clinical utility of new plasma biomarkers, such as C-reactive protein (CRP),[160,161,169,170] myeloperoxidase (MPO),[160,161,171] galectin 3 (gal-3) (fibrosis marker),[160,161,172] BB glycogen phosphorylase (GPBB),[173,174] placental growth factor (PlGF),[160,161,171] growth differentiation factor (GDF-15),[160,151] endothelin-1,[175] as well as circulating microRNAs[176,177] in the monitoring of myocardial toxicity of adjuvant breast cancer therapy.

Putt *et al*.[161] assessed the role of selected-biomarkers [hs-cTnI, NT-proBNP, hsCRP, GDF-15, MPO, PlGF, soluble fms-like tyrosine kinase-1 (sFlt-1) and gal-3] in the prediction of early cardiotoxicity in 78 patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab, and they found a significant correlation between the analysed markers (except for NT-proBNP and gal-3) and the development of cardiotoxicity in the 3rd month of therapy. After 15 months of follow-up, elevated levels hsTnI and, to a lesser extent, GDF-15 and PlGF were observed. Finally, the authors concluded that the analysis of three of the aforementioned biomarkers (MPO, PlGF, and GDF-15) could improve the identification of patients who are at risk of cardiotoxicity. However, in this study, no such relationship was found for troponin I, NT-proBNP, or hsCRP.[161] Ky *et al*.[160] have demonstrated that MPO could be used in combination with TnI to identify patients who had a significantly higher risk of cardiotoxicity as a result of combination anthracycline therapy. Patients with MPO levels in the 90th percentile had a predicted cardiotoxicity rate of 36.1% after 15 months.[160]

A pilot study performed by Gullo *et al*.[171] assessed the role of selected biomarkers (VEGF, endothelial growth factor; PlGF, placental growth factor; MPO, myelopreoxidase, cTnI, troponin I) in the detection of early cardiotoxicity in patients with early stage of HER-2 negative breast cancer treated with bevacizumab in combination with docetaxel and cyclophosphamide as an adjunctive therapy. In their study, only elevated PlGF level at baseline correlated with a subsequent significant decrease in LVEF (especially in the third cycle of chemotherapy). The decrease in VEGF concentration after 6 months correlated with higher LVEF assessed at the same time in comparison with LVEF assessed at the beginning of the study. In turn, Onitilo *et al*.[172] showed that regular monitoring of hs-CRP could be beneficial for the identification of women with early stage of breast cancer and a low risk of asymptomatic trastuzumab-induced cardiotoxicity. However, this study failed to reveal such relationship for troponin I and BNP.[171]

Recently, more and more studies have been devoted to the assessment of microRNAs as markers of early cardiotoxicity.[176–185] Small non-coding single-stranded RNAs —microRNAs (miRs)—regulate gene expression at the post-transcriptional level under both physiological and pathophysiological conditions. Therefore, they play an important role in the regeneration of various tissues and organs, including myocardium.[182,183,184] The repair of myocardial cells involves the regulation of apoptosis, proliferation, metabolism, angiogenesis, and aging by miRs.[189] MiR-590 promotes cardiac regeneration by activating cardiomyocyte proliferation,[176] a set of specific miRs (miR-1, miR-133, miR-208, and miR-499) is efficient at converting cardiac fibroblasts into cardiomyocytes,[183] while miR-34a inhibits heart regeneration via the induction of apoptosis.[176] The change in plasma level of circulating miR, including miR-1, miR-34a, and miR-150 after the exposure to anthracyclines, occurs before myocardial cell damage.[176,184,185] Therefore, circulating miRs may pose early markers of myocardial damage, for example, after chemotherapy or ischaemia, the detection of which is possible even before the increase in other biomarkers, such as cardiac troponins or natriuretic peptides.[177,184,185]

New plasma biomarkers can pose a promising tool for detecting early cardiotoxicity and for the identification of patients who require increased cardiovascular monitoring or cardioprotective therapy.

Studies and results presenting new biomarkers with potential significance in the detection of early cardiotoxicity are summarized in *Table 4*.[160,161,169–177]

Genetic polymorphisms predictors of cardiotoxicity

The aforementioned new echocardiographic parameters and plasma biomarkers are considered as useful in the detection of early cardiotoxicity. They allow the identification of patients with pre-existing myocardial damage before a decrease in LVEF or the appearance of heart failure symptoms. However, this myocardial damage has irreversibly activated compensatory mechanisms and reserves in the heart muscle, which can only be slowed down by cardioprotective therapy.

Therefore, the search for a genetic predisposition to the toxic effects of chemotherapy or resistance to the adjuvant treatment of breast cancer seems to be an important direction of current clinical research. It could help to design more individualized treatment regimens with a minimal risk of cardiotoxicity for the patient. Anthracyclines, due to their high anti-cancer efficacy, are still the basis of breast cancer treatment.[5,8,133] The limitation of their use is associated with the dose-dependent cardiotoxicity, which may occur even without exceeding the total dose, but also at lower doses (150 mg/m^2) that are considered as safe.[186] This suggests the existence of inter-individual differences in the pharmacogenetics of anthracycline metabolism, which may have a significant impact on the anti-tumour efficacy and toxicity of these chemotherapeutics.[187]

Genes encoding proteins, which play an important role in anthracycline metabolic pathway, include, but are not limited to, genes encoding drug metabolizing enzymes and proteins involved in drug transport.[188] Two types of anthracycline, efflux transporter proteins (ABC, ATP-binding cassette family) and influx transporters (SLC, solute carrier family transporter), have been identified.[188] Transporters belonging to the ABC family[189] are transmembrane ATP-dependent pumps present, among others, in the liver, kidneys, intestines, as well as in the heart, lungs, and reproductive organs. They regulate the distribution of endogenous metabolites and xenobiotics, including chemotherapeutics and also participate in their excretion from the body. In the heart, they participate in the protection of this organ against toxic compounds and drug-induced oxidative stress.[189] Moreover, proteins belonging to the ABC family are associated with cancer cell resistance to chemotherapy (MRP1, multidrug resistance-associated protein 1).[190]

Influx transporters (SLC, solute carrier family transporter) are involved in the transport of substances and xenobiotics to the cell.[188] Furthermore, SLC is involved in anthracycline uptake by cancer cells and other tissues, including cardiomyocytes.[188] The role of polymorphisms within genes encoding transporter proteins (ABC and SLC) in anthracycline-induced cardiotoxicity or cancer cell resistance to cancer treatment is currently the subject of numerous studies since such polymorphisms may affect the efficacy and safety of chemotherapy.[191–195]

The correlation between SLC28A3 rs7853758 and rs885004 polymorphisms and anthracycline toxicity has been demonstrated in two cohort studies involving paediatric anthracycline-treated patients.[191,192] However, a study of adult patients with breast cancer failed to show such relationship in case of SLC28A3 rs7853758 polymorphism.[193] In turn, in a study of patients with breast cancer,[194] the presence of SLC22A16 polymorphisms was associated with lower (rs714368, rs6907567, and rs723685) or greater (rs12210538) anthracycline toxicity. In a study of adult patients treated with anthracyclines for acute myeloid leukaemia, the presence of ABCG2 rs2231142 polymorphism was associated with a higher risk of cardiotoxicity.[195]

The aforementioned studies suggest that genotyping combined with clinical image analysis can help to identify patients predisposed to oncological treatment-induced cardiotoxicity. This method also enables the individualization of both the treatment plan and cardiovascular monitoring.

Clinical relevance and novelty aspects in cardiotoxicity of adjuvant breast cancer treatment breast cancer cardiotoxicity

Adjuvant therapy for breast cancer (both systemic and radiation therapy) is necessary to reduce morbidity and mortality. Unfortunately, its cardiotoxicity is a limitation of this therapy. The main reason is that its use can lead to the development of heart failure and may negatively affect quality of life and prognosis. Therefore, the knowledge of the mechanisms of toxic effects of modern oncological treatment methods and the optimization of cardiovascular risk factors is of high importance. The American (ASCO and ASE) and European (ESMO, ESC, and EACVI) experts in oncology and cardiology offer general guidelines for monitoring high risk patients for cardiotoxicity. A number of risk factors are common to both breast cancer and cardiovascular disease (CVD). The cardiac risk factors and pre-existing CVD can have also an influence on cancer treatment methods.[196] During breast cancer treatment, surveillance, prevention, and secondary management of cardiotoxicity are crucial. Thereafter, long-term post-treatment monitoring for late cardiotoxicity and even non-treatment-related development of CVD is essential. Modifications of risk factors owing to blood pressure control, diabetes mellitus management, a proper lipid profile as well as a promoting a healthy diet, a healthy weight, physical activity and abstinence from tobacco, can prevent about 80% CVD.[197] Risk factors for breast cancer have only been discussed more recently, but there is growing awareness that through risk factor modification, some cases of breast cancer might be prevented.[198] The time when best start cardioprotection is still not clearly specified. Moreover, the use of cardiovascular drugs such as beta-blockers, angiotensin-converting-enzyme inhibitors (ACEIs), and angiotensin

Table 4 New biomarkers potentially relevant for the detection of early cardiotoxicity[160,161,169–177]

Study	Cancer type	No. of patient cases	Median age (year)	Cancer therapy	Time interval	New biomarkers								
						hsCRP	MPO	Endothelin-1	GPBB	VEGF	PIGF	GDF-15	Gal-3	miRNA
Ky *et al.*[160]	Breast cancer	78	50	Doxorubicin and trastuzumab	0, 3, 6, and 15 (months)	NSC	SC	-	-	-	NSC	NSC	NSC	-
Putt *et a.*[161]	Breast cancer	78	49	Doxorubicin, taxanes, and trastuzumab	0, 3, 6, 9, 12, and 15 (months)	SC	SC	-	-	-	SC	SC	NSC	-
Morris *et al.*[169]	Breast cancer	95	46	Doxorubicin, cyclophosphamide, paclitaxel trastuzum, and ablapatinib	0, 2, 6, 9, and 18 (months)	SC	-	-	-	-	-	-	-	-
Onitilo *et al.*[170]	Breast cancer	54	>18	Trastuzumab	Every 3 weeks with each cycle of trast	SC	-	-	-	-	-	-	-	-
Gullo *et al.*[171]	Breast cancer	106	52	Bevacizumab and docetaxel cyclophosphamide	0, 3, and 6 (months)	-	SC	-	-	SC	SC	-	-	-
Bulten *et al.*[172]	Breast cancer	59	52	Anthracyclines	1 year after anthracycline treatment	-	-	-	-	-	-	-	SC	-
Horacek *et al.*[173]	Acute leukaemia	24	>18	Anthracyclines	0 and 6 (months)	-	-	-	SC	-	-	-	-	-
Horacek *et al.*[174]	Acute leukaemia	47	>18	Anthracyclines	Before CT/HD-CT, after first CT with ANT, after last CT with ANT	-	-	-	SC	-	-	-	-	-
Zver *et al.*[175]	Multiple myeloma	30	NR	Cyclophosphamide and melphalan	0, 15 days, 3 months	-	-	SC	-	-	-	-	-	-
Rigaud *et al.*[176]	Breast cancer	56	49.9 ± 3.3	Doxorubicin	In 4 cycles for 3 months	-	-	-	-	-	-	-	-	SC miR-1
Qin *et al.*[177]	Breast cancer	363	NR	Epirubicin/ cyclophosphamide follow by docetaxel	0, 3, 6, 9, and 12 (months)	-	-	-	-	-	-	-	-	SC* miR-17-5p miR-20a

ANT, anthracyclines; CT, chemotherapy; GPBB, glycogen phosphorylase Isoenzyme BB; HD-CT, high dose chemotherapy; MPO, myeloperoxidase; NR, not reported; NSC, no significant correlation with cardiotoxicity or cardiac dysfunction; PlGF, placental growth factor; SC*, significant correlation with lower cardiotoxicity or cardiac dysfunction; SC, significant correlation with cardiotoxicity or cardiac dysfunction; trast, trastuzumab; VEGF, vascular endothelial growth factor.

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receptor blockers, statins, or aerobic exercise to prevent cardiotoxicity is controversial and based on a limited number of clinical trials.

In meta-analysis included randomized clinical trials of adult patients that underwent chemotherapy and neurohormonal therapies (beta-blockers, ACEIs, angiotensin receptor blockers, and mineralocorticoid receptor antagonists) observed association between treatment with cardiovascular drug and higher LVEF in follow-up among cancer patients receiving chemotherapy.[199] In turn, the CECCY (Carvedilol Effect in Preventing Chemotherapy Induced Cardiotoxicity) trial tested the use of beta-blocker (carvedilol) versus placebo in 200 patients with breast cancer and normal LVEF receiving anthracycline 240 mg/m^2. Carvedilol had no impact on the incidence of early onset of LVEF reduction.[200] Statins are another class of drugs that have been evaluated for their cardioprotective role in cancer patients exposed to cardiotoxic agents. In retrospective study of Seicean *et al*., women receiving uninterrupted statin therapy throughout the approximately 3 year follow-up period demonstrated significantly lower hazard ratios (HR: 0.3; 95% CI: 0.1–0.9; P = 0.03) for development of heart failure as compared with the control groups. More studies regarding the use of statins are emerging in the field of cardio-oncology.[201]

In prospective analysis of 2973 non-metastatic breast cancer women (8.6 year median follow-up), routine exercise of ≥9 MET-hour/week was associated with a reduction in CV events (new diagnosis of coronary artery disease, valve abnormality, arrhythmia, stroke, or CVD death).[202] Furthermore, there are data suggesting those who start physical activity after a diagnosis of breast cancer have a lower risk of death in general.[203] The American Heart Association (AHA) recommend physical activity as an individualized cardiac rehabilitation intervention for those most at risk of developing cardiotoxicity[204] and the European Society for Medical Oncology (ESMO) to recommend exercise for all cancer survivors.[24] However, further large-scale studies are needed to determine specific exercise recommendations based on population and risk stratification.

Echocardiography, electrocardiography as well as with the analysis of the concentration of cardio-specific serum biomarkers (such troponin T and NT-proBNP) are the first-line diagnostic tool for the assessment of the cardiovascular system in such patients. Elevated troponin levels predict LV dysfunction in patients receiving cancer therapy. Assessment of troponin levels may be a screening test to identify patients who require referral to cardio-oncology units and benefit from preventive strategies.[205]

The low sensitivity of left ventricular ejection fraction assessment limits its use in preventive strategy. New imaging parameter, such as GLS, is more useful echocardiographic method for the detection of early myocardial damage. Moreover, the assessment of other parameters of myocardial function, which have not been included in current recommendations such right ventricular function, changes in left ventricular diastolic function or changes in the volume and function of the left atrium may be important in predicting the subclinical cardiotoxicity of radiotherapy and chemotherapy.

The search for and the analysis of new cardio-specific biomarkers in serum, such as C-reactive protein (CRP), myeloperoxidase (MPO), BB glycogen phosphorylase (GPBB), placental growth factor (PlGF), as well as circulating microRNAs in the monitoring of myocardial toxicity of adjuvant breast cancer therapy, can pose a promising tool for detecting early cardiotoxicity and for the identification of patients who require increased cardiovascular monitoring or cardioprotective therapy. Moreover, a genetic predisposition to the toxic effects of chemotherapy or resistance to the adjuvant treatment of breast cancer seems to be an important direction of current clinical research. The genes encoding proteins, which play an important role in anthracycline metabolic pathway, in particular presented by us genes encoding proteins involved in drug transport, suggest that genotyping combined with clinical condition and imaging biomarkers may become a useful method for identifying patients at risk of developing cardiotoxicity. It could help to design more individualized treatment regimens with a minimal risk of cardiotoxicity for the patient.

Conflict of interest

The authors declare no conflict of interest.

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