





Is it possible to prevent chemotherapy-induced heart failure with cardiovascular drugs - the review of the current clinical evidence

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Abstract: Cardiovascular diseases and cancer are the most common death causes in the USA and Europe. Moreover, many patients suffer from both of these conditions – a situation which may result from cardiotoxicity of anticancer treatment. In order to reduce the severity of this adverse effect, various methods have been proposed, including the usage of new drug forms and less toxic analogs, omitting the combinations of potentially cardiotoxic drugs and introducing potential cardioprotective agents to the therapy. However, prevention of cardiotoxicity still seems to be insufficient. The article reviews the results of current studies on the use of cardiovascular drugs in the prevention of cardiotoxicity. Based on this knowledge, the most promising cardioprotective drugs seem to be carvedilol, nebivolol, enalapril, and candesartan, as they prevent heart remodeling and correct elevated resting heart rate, which directly affects mortality. Alternatively, in case of adverse reactions, statins might be considered.

Keywords: chemotherapy, cardiotoxicity, heart failure, prevention

Introduction

Cardiovascular diseases and cancer are the most common death causes in the USA and Europe, although long-term survival of oncological patients has increased in the last years, reaching 64% of 5-year survival rate, 41% of 10-year survival rate and 15% of 20-year survival rate. Moreover, many patients suffer from both of these conditions – a situation which may result from cardiotoxicity of anticancer treatment.^{1,2} The most frequent symptom of such cardiotoxicity is LVEF (left ventricular ejection fraction) reduction which may indicate the development of left ventricular dysfunction and lead to congestive heart failure. Other cardiotoxicity symptoms include arrhythmias, changes in blood pressure or cardiomyopathy. Data from United Network for Organ Sharing (UNOS) and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) indicate that 0.5% to 2.5% patients with left ventricular assist devices and orthotopic heart transplantation had cancer treatment-related cardiomyopathy.^{3,4}

To address the problem of cardiotoxicity, various methods have been introduced, including the application of high-sensitivity diagnostic methods, the use of new forms and less toxic analogs of chemotherapeutics, and coadministration of dexrazoxane.^{5–7} Nevertheless, the use of cardiovascular drugs for cardioprotection of oncological patients has not been recommended so far.^{8,9} Only the “2016

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European Guidelines on cardiovascular disease prevention in clinical practice” stated that early preventive treatment should be applied to achieve maximum efficacy in counteracting anthracycline-induced cardiotoxicity in high-risk patients.¹⁰ Cardiovascular drugs have been studied for many years as potential agents preventing cardiotoxicity of oncological treatment.^{11–13} Therefore, the subject of the presented article is to review the results of clinical trials assessing the cardioprotection of patients undergoing oncological treatment.

Methods

PubMed database was searched using the following terms: cardiotoxicity, prevention, RAA system drugs, β -blockers, trimetazidine, ACEI, ARB, statin, ivabradine, coenzyme Q10, ranolazine, aldosterone antagonist.

β -blockers

Nebivolol

Cardioprotective effect of nebivolol was confirmed in an experimental model of doxorubicin-induced cardiac toxicity by Imbaby et al. They have found that it improved survival rate, ECG (electrocardiogram) parameters, cardiac enzymes, oxidative stress, apoptosis, and histopathological picture which are potentiated by adding a low dose of curcumin.¹⁴ The protective effect of 5 mg daily dose of nebivolol in breast cancer patients receiving anthracycline-based chemotherapy was also assessed in the randomized, double-blind, placebo-controlled clinical study by Kaya et al (Table 1). At 6-month after chemotherapy, echocardiographic measurements of left ventricular end-systolic diameters (LVESD) and left ventricular end-diastolic diameters (LVEDD) remained unchanged in the nebivolol group (LVESD: 30.4 \pm 3.5 to 31.0 \pm 3.6 mm, $p=0.20$; LVEDD: 47.0 \pm 4.4 to 47.1 \pm 4.0 mm, $p=0.93$) in contrast to significant increase in the control group. The placebo group had also lower LVEF (left ventricular ejection fraction) than the nebivolol group (57.5 \pm 5.6% vs 63.8 \pm 3.9%, $p=0.01$). The level of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) remained static in the nebivolol group while it significantly increased in the placebo group.¹⁵

Carvedilol

In the first clinical randomized trial with carvedilol (12,5 mg once-daily), performed by Kalay et al (Table 1), it was found that 6-month treatment maintained LVESD, LVEDD, and systolic function compared with placebo.

The interventions were initiated prior to the start of chemotherapy and continued for six months.¹⁶ Similar results were obtained by Elitok et al (Table 1) in a group of female patients using the same dose of the drug. The authors have found that septal and lateral systolic strain and strain rate values were significantly lower in control patients compared to the carvedilol group.¹⁷

Zamani et al (Table 1) carried out a randomized, controlled trial where patients with lymphoma or breast cancer were administered carvedilol. They observed that a lower dose of carvedilol (6,25 mg/day) did not have a significant effect on the prevention of diastolic and systolic dysfunction, contrary to the dose 12.5 mg/day. These results suggested that the cardioprotective effect was dose-dependent.¹⁸

Recently published CECCY trial (Table 1) was conducted on 192 patients with breast cancer but without cardiovascular diseases, receiving cyclophosphamide, doxorubicin, and paclitaxel. It was found that carvedilol, initially with a dose of 3.125 mg twice a day to a maximum dose of 25 mg every 12 hrs, affected only troponin I, B-type natriuretic peptide, and diastolic dysfunction. The study did not find any significant effect of carvedilol on LVEF. Symptomatic hypotension was reported in 3 patients in the carvedilol group; one of them was withdrawn from the study.¹⁹

A meta-analysis of 8 randomized controlled trials carried out by Kheiri et al (Table 1), assessing changes in ejection fraction of patients treated with anthracyclines, revealed that carvedilol protected the patients from LVEF reduction (mean differences between carvedilol and placebo groups: 2.41%). The authors concluded that prophylactic use of carvedilol might have a cardioprotective effect, reducing the early onset of left ventricular dysfunction.²⁰

Bisoprolol

During the MANTICORE 101–Breast trial (Table 1), it was found that bisoprolol administered to patients treated with trastuzumab (who received a non-anthracycline-based chemotherapy), titrated weekly to 10 mg, attenuated trastuzumab-mediated declines in LVEF but did not prevent ventricular remodeling. No significant adverse effects were noted during the study; lower heart rate was observed after completed chemotherapy.²¹

Metoprolol

Georgakopoulos et al (Table 1), in a randomized control trial with long (36 months) follow-up observed decreased

Table 1 Clinical trials assessing the use of cardiovascular drugs in cardioprotection

Authors	Design	Drug (dose, administration)	Patients			Imaging techniques	Biochemical analysis	Study limitations
			Number of patients	Type of cancer	Oncological therapy			
Kaya et al (2013) ¹⁵	Prospective, randomized, double-blind, placebo-controlled study	Nebivolol 5 mg daily drug was given orally at a dose of 5 mg/day in the morning for 7 consecutive days before chemotherapy and was continued for 6 months	45 (27 treatment group + 18 placebo group)	Breast cancer	Adriamycin/epirubicin, cyclophosphamide, 5-fluorouracil (5-FU) and docetaxel (DCT)	Transthoracic echocardiographic	NT-pro-BNP	Small, single center study Only female patients Only early-onset cardiac toxicity was assessed
Kalay et al (2006) ¹⁶	Prospective, randomized, single-blind, and placebo-controlled trial.	Carvedilol 12.5 mg once-daily for 6 months. 12.5 mg once-daily oral carvedilol was started before chemotherapy and maintained for 6 months during chemotherapy. All patients received chemotherapy at a mean of every 3 weeks	50 (25 treatment group + 25 placebo group)	Breast cancer, lymphoma, other cancer types	Adriamycin or epirubicin	Echocardiography		Small number of patients. Mortality difference between treatment and control group was not significant. Only early-onset cardiac toxicity was assessed

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Table 1 (Continued).

Authors	Design	Drug (dose, administration)	Patients			Imaging techniques	Biochemical analysis	Study limitations
			Number of patients	Type of cancer	Oncological therapy			
Eltok et al (2014) ¹⁷	Prospective, randomized controlled study	Dose of 12.5-mg oral carvedilol prior to computed tomography, and followed by an oral carvedilol maintenance dose of 12.5 mg daily for 6 months during chemotherapy	80 (40 treatment group + 40 control group)	Breast cancer	Doxorubicin	Echocardiography Strain imaging		Open label design Relatively small sample size Only female patients Only early-onset cardiac toxicity was assessed
Zamani et al (2018) ¹⁸	Prospective, randomized, double-blind placebo-controlled study	Carvedilol (6.25 or 12.5 mg daily); started 24 hours before chemotherapy and lasted for 4 months	66; two treatment groups with 22 patients (6.25 or 12.5 mg of carvedilol daily) vs one placebo group (22 patients)	Breast cancer, lymphoma	Doxorubicin or epirubicin	Echocardiography.		Relatively small sample size Only early-onset cardiac toxicity was assessed

(Continued)

Table 1 (Continued).

Authors	Design	Drug (dose, administration)	Patients			Imaging techniques	Biochemical analysis	Study limitations
			Number of patients	Type of cancer	Oncological therapy			
Avila et al (2018) ¹⁹	Prospective, randomized, double-blind, placebo-controlled study	Carvedilol administered in a progressive manner with incremental dosing at 3-week intervals beginning with a dose of 3.125 mg twice a day, which was then increased to 6.25 mg, then to 12.5 mg, to a maximum dose of 25 mg every 12 h or until the appearance of intolerable symptoms or heart rate ≤ 60 beats/min or systolic blood pressure < 110 mm Hg. Continued until completion of chemotherapy	192 (96 treatment group + 96 placebo group)	HER2-negative breast cancer	Doxorubicin, cyclophosphamide, taxane	Transthoracic echocardiography	TnI, B-type natriuretic peptide (BNP)	Single center study Only female patients The incidence of early onset cardiotoxicity lower than expected \rightarrow might reduce the statistical power of the study Optimization of carvedilol dosing during chemotherapeutic treatment might result in reaching target dose at a later stage of chemotherapy. The maximum tolerated dose of carvedilol and placebo less than expected. The interobserver variability might have influenced the repeated LVEF measurements As the primary endpoint was not met, any statements related to the secondary endpoints need to be carefully interpreted Short follow-up period (6 months) \rightarrow only early-onset cardiac toxicity was assessed
Kheiri et al (2018) ²⁰	Metaanalysis (8 randomized controlled trials)	Carvedilol	633	Breast cancer, lymphoma, lymphoreticular malignancy, various malignancies	Anthracyclines	Transthoracic echocardiography		Missing effect size and power calculations in most trials Single-blinded, and single-center trials Limited number of heterogeneous female patients, many with breast cancer.

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Table 1 (Continued).

Authors	Design	Drug (dose, administration)	Patients			Imaging techniques	Biochemical analysis	Study limitations
			Number of patients	Type of cancer	Oncological therapy			
Pituskin et al (2017) ²¹	Prospective, double-blinded, placebo-controlled trial	Bisoprolol (2.5 mg titrated to 10 mg daily), perindopril (2 mg titrated to 8 mg daily); initiated within 7 days before the start of trastuzumab and were titrated weekly as tolerated over 3 weeks, with daily target doses of perindopril 8 mg, bisoprolol 10 mg. Study medication was given for the duration of trastuzumab adjuvant therapy	94 (64+30): 33 patients on perindopril; 31 on bisoprolol; 30 on placebo	HER2-positive early breast cancer	Trastuzumab, anthracyclines, cyclophosphamide, docetaxel, 5-fluorouracil	Cardiac magnetic resonance imaging	Only female patients Relatively small sample size Unclear long-term significance of LV remodeling Younger population, with fewer cardiovascular risk factors, which may lead to underestimation of cardioprotective effect compared with a real-world setting	
Georgakopoulos et al (2010) ²²	Prospective, parallel-group, randomized, controlled study	Enalapril (11±0.68 mg daily) or metoprolol (88±3.1 mg daily)	125: 42 patients on metoprolol, 43 on enalapril; 40 patients in the control group	Hodgkin lymphoma, non-Hodgkin lymphoma	Doxorubicin, bleomycin, vinblastine, decarbazine, rituximab, cyclophosphamide, vincristine, prednisolone	Echocardiography	Open-label design Lack of placebo	

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Table 1 (Continued).

Authors	Design	Drug (dose, administration)	Patients			Imaging techniques	Biochemical analysis	Study limitations
			Number of patients	Type of cancer	Oncological therapy			
Gulati et al (2016) ²³	Prospective, randomized, placebo-controlled, double-blind clinical trial	Candesartan titrated from 8 mg to 32 mg daily, metoprolol titrated from 50 mg to 100 mg daily; drugs started prior to initiation of chemotherapy	130: 30 patients on candesartan + metoprolol; 32 on candesartan + placebo; 32 on metoprolol + placebo; 32 on placebo	Early breast cancer	5-fluorouracil, epirubicin, cyclophosphamide	Cardiac magnetic resonance imaging Transthoracic echocardiography	Tnl, BNP	Only female patients Lack of follow-up information beyond the adjuvant therapy period Many patients, with indications for treatment with β -blockers or RAA inhibitors Limited statistical power
Cardinale et al (2006) ²⁵	Prospective, randomized clinical study	Enalapril started 1 month after HDC and continued for 1 year. Enalapril was administered at an initial dose of 2.5 mg once daily and was increased gradually through 3 steps to 20 mg once daily (5, 10, and 20 mg, respectively)	114 (56 treatment group + 58 control group) treatment group: patients who showed a troponin I increase soon after high dose chemotherapy	Acute myeloid leukemia, breast cancer, Ewing's sarcoma, Hodgkin's disease myeloma, non Hodgkin's lymphoma.	Cytarabine, carmustine, etoposide, melphalan, daunorubicin, carboplatin, dexamethasone, ifosfamide, idarubicin, mitoxantrone, taxotere, epirubicin, cyclophosphamide, anthracyclines	Echocardiography	Tnl	Lack of placebo Open-label follow-up. The lack of prespecified and rigorously defined clinical end points Several oncological dis-eases and chemotherapeutic regimens included in the study

(Continued)

Table 1 (Continued).

Authors	Design	Drug (dose, administration)	Patients Number of patients	Type of cancer	Oncological therapy	Imaging techniques	Biochemical analysis	Study limitations
Liu et al (2013) ²⁹	Prospective randomized, controlled study	Carvedilol (5 mg daily titrated to 10 mg daily) combined with candesartan (2.5 mg daily) starting at first cycle	40 (20 treatment group + 20 control group)	Breast cancer	Anthracyclines	Echocardiography Electrocardiogram	Troponin	Relatively small sample size Short follow-up period

(Continued)

Table 1 (Continued).

Authors	Design	Drug (dose, administration)	Patients			Imaging techniques	Biochemical analysis	Study limitations
			Number of patients	Type of cancer	Oncological therapy			
Boekhout et al (2016) ³⁰	Randomized, placebo-controlled clinical study	Candesartan 16 mg daily for the first week, changed to 32 mg daily since the 2nd week; started at the same day as the first trastuzumab administration and continued until 26 weeks after completion of trastuzumab treatment	206 (103 treatment group + 103 control group)	Early breast cancer	Anthracyclines, trastuzumab	Echocardiography	High-sensitivity troponin T (hs-TnT), NT-proBNP, ERBB2 genotyping	Only female patients Lack of a universally used definition of trastuzumab-related cardiotoxic effects
Cadeddu et al (2010) ³¹ Dessi et al (2013) ²⁸	Prospective randomized placebo controlled study	Teimisartan 40 mg daily, starting 1 week before chemotherapy	49 (25 treatment group + 24 control group)	Different tumor types (non-Hodgkin lymphoma, cancer of endometrium, salivary gland, breast, ovary, lung)	Epirubicin	Echocardiography Strain and strain rate (SR) imaging	IL-6, TNF- α , ROS, glutathione peroxidase (GPx)	Relatively small sample size Short follow-up
Akpek et al (2015) ³²	Prospective, randomized, placebo-controlled, and double-blind study	Spirolactone 25 mg daily, initiated 1 week before the start of chemotherapy	83 (43 treatment group + 40 control group)	Breast cancer	Adriamycin, epirubicin, cyclophosphamide, docetaxel, 5-flourouracil, paclitaxel, docetaxel	Transthoracic echocardiography	NT-proBNP TnI, total antioxidant capacity, total oxidative capacity	Only female patients Relatively small sample size

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Table 1 (Continued).

Authors	Design	Drug (dose, administration)	Patients	Patients			Imaging techniques	Biochemical analysis	Study limitations
				Number of patients	Type of cancer	Oncological therapy			
Seicean et al (2012) ³³	An Observational Cohort Study retrospectively istudy	Patients receiving uninterrupted statin throughout the follow-up period	201 (67 treatment group + 134 control group)	Breast cancer	Anthracycline-based chemotherapy. trastuzumab	Echocardiography		Only female patients Single center study Concomitant use of β -blockers and statins by nearly half of the patients Use of statins, ACE inhibitors, beta-blockers, and insulin at or before the study entry date. Medication status during follow-up is not known by the clinician at baseline The use of statins may have been affected by various factors which result in potential bias	
Acar et al (2011) ³⁴	Prospective randomized controlled study	Atorvastatin 40 mg daily, started before chemotherapy and continued for 6 months	40 (20 treatment group + 20 control group)	Non-Hodgkin's lymphoma, multiple myeloma, lekuemia	Vincristine, cyclophosphamide, methotrexate, prednisolone, dexamehasone, adriamycin, idarubicin	Echocardiography		Small sample size Lack of placebo group Limited measures of cardiac dysfunction Short follow-up \rightarrow only early-onset cardiac toxicity was assessed	
Chotenimitkhun et al (2015) ³⁵	Prospective controlled study	Atorvastatin (5 patients), simvastatin (9 patients); average dose 40 ± 5 mg daily (5 mg to 80 mg)	51 (14 treatment group + 37 control group)	Breast cancer, leukemia, lymphoma	Doxorubicin, daunorubicin, epirubicin, cyclophosphamide, tamoxifen, trastuzumab	Cardiovascular magnetic resonance imaging		Small sample size Dissimilar participant groups could influence LVEF Despite association between the statin use and attenuation of LVEF declines after chemotherapy, causality cannot be inferred Short follow-up period	

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Table 1 (Continued).

Authors	Design	Drug (dose, administration)	Patients Number of patients	Type of cancer	Oncological therapy	Imaging techniques	Biochemical analysis	Study limitations
Tallarico et al (2003) ⁴¹	Prospective randomized study	Group 1: trimetazidine (60 mg daily) + dextrazoxane (100 mg daily); group 2: trimetazidine (60 mg daily); group 3: dextrazoxane (100 mg daily)	61: 15 (group 1) + 22 (group 2) + 24 (group 3)	Breast cancer	Epirubicin, doxorubicin	Echocardiography		No standard definition of anthracyclines cardiotoxicity existed at the time of study. Interobserver and intraobserver variability of the 2-dimensional echocardiographic measurements Relatively small sample size

frequency of heart failure in the group receiving metoprolol treatment. However, observed difference was not statistically significant.²² Gulati et al (Table 1) have found in the PRADA study that 78±32 mg daily metoprolol did not affect LVEF, ECV (extracellular volume) fraction, total ECV, or total cellular volume in patients on anthracycline therapy. The therapy was safe, with no severe adverse reactions and no patients withdrew from the study.^{23,24}

Angiotensin-converting enzyme inhibitors

Enalapril

Cardinale et al (Table 1) used enalapril (20 mg/day) in a group of 56 cancer patients receiving high-dose chemotherapy. The treatment was started one month after the last chemotherapy cycle and was continued for one year. The study revealed persistently high TnI increase, associated with a greater LVEF reduction, in the control group (58 patients who did not receive enalapril). Administration of enalapril prevented a reduction in LVEF and an increase in end-diastolic and end-systolic volumes; moreover, the drug was well tolerated in most patients.²⁵ These results were the premise for conducting research during which the drug was administered simultaneously with other cardiovascular agents commonly recommended as initial treatment of heart failure. First such study was the OVERCOME trial (Table 1), carried out on 90 patients with leukemia or malignant hemopathies, which revealed that patients receiving enalapril and carvedilol had a lower incidence of death and heart failure after intensive chemotherapy; the treatment also protected from negative changes in LVEF. There was no interaction between the drugs concerning the effect on LVEF and troponin I (TnI) increase. The study also confirmed the safety of such treatment: only three patients discontinued enalapril, while two patients stopped carvedilol and one withdrew from taking both drugs.²⁶

Perindopril

Perindopril was assessed in MANTICORE study (Table 1) - the first randomized, placebo-controlled trial for the prevention of trastuzumab-mediated cardiotoxicity. The drug was titrated weekly to 8 mg and attenuated trastuzumab-mediated declines in LVEF. However, it did not prevent ventricular remodeling. No significant adverse effects were

noted during the study; lower blood pressure was observed in post-chemotherapy assessment.²⁷

Angiotensin 2 receptor blockers

Candesartan

According to the results of PRADA study (Table 1), candesartan (26±9 mg daily) did not reduce circulating TnI (increased during anthracycline therapy) showing that angiotensin receptor blockers (ARB) had no effect on direct anthracyclines cardiotoxicity. However, they can affect remodeling of the myocardium which takes place after cardiac injury: angiotensin II directly stimulates protein synthesis in myocytes, causes myocyte hypertrophy, and induces an increase in left ventricular mass independent of pressure overload. The researchers observed that patients receiving candesartan had significantly lower LVEF decline compared to the placebo group. The safety profile of the treatment was good, with no serious adverse effects and no patients withdrawn.²⁸ The study has also confirmed the effect of candesartan on the dose-dependent anthracycline-induced increase in myocardial ECV - it was found that concomitant treatment with candesartan led to a reduction of left ventricular total cellular volume.²⁴ Additionally, Liu et al (Table 1) observed that low-dose carvedilol (from 2.5 mg twice a day at first cycle to 5 mg twice a day) combined with candesartan (2.5 mg once a day) in patients on anthracycline therapy did not prevent LVEF decrease, however it resulted in protection from intracellular damage (only 10% of the group had significantly higher expression of troponin) and ECG abnormalities.²⁹

On the other hand, Boekhout et al (Table 1) did not confirm the protective effect of candesartan (32 mg/day) in patients with breast cancer receiving anthracycline-containing chemotherapy followed by trastuzumab. The study has also found a single nucleotide polymorphism (SNP) Ala1170Pro in ERBB2 gene associated with the probability of cardiotoxicity.³⁰

Telmisartan

Cadeddu et al (Table 1) have found that 40 mg daily telmisartan (started one week before chemotherapy) in patients taking epirubicin resulted in strain rate normalization and reduction in epirubicin-induced radical species: at 200 mg/m² epirubicin, strain rate in both telmisartan and placebo groups was reduced, however the decrease observed in the placebo group was significantly greater. Moreover, after an increase in cumulative epirubicin dose,

strain rate in the telmisartan group increased, almost reaching the baseline level.³¹ The long-term positive effect was confirmed in an 18-month follow-up study: the telmisartan group maintained the strain rate level, while a further decrease was observed in the placebo group. Moreover, the treatment protected the patients from an elevation of proinflammatory cytokines (interleukin-6: IL-6, tumor necrosis factor- α : TNF- α) and reactive oxygen species (ROS). Although the drug was well tolerated, two patients developed significant hypotension which resulted in temporary reduction of telmisartan dose (from 40 to 20 mg daily); after two weeks the full dose was restored.²⁸

Aldosterone antagonists

The renin-angiotensin-aldosterone system (RAAS) has a significant effect on remodeling the myocardium in post-myocardial damage. Therefore, aldosterone antagonists have been shown to protect cardiac muscle against anthracycline-induced cardiomyopathy by preserving LVEF, LVEDD, and LVESD. Akpek et al (Table 1) carried out a prospective, randomized, placebo-controlled, double-blind study on 83 patients with breast cancer, treated with an anthracycline (adriamycin, epirubicin) and spironolactone (25 mg/day) or placebo, confirming the changes in cardiac biomarkers and echocardiography (ECHO) parameters. TnI levels increased significantly in both groups during the treatment period but the much higher level was observed in the control group, while the serum NT-proBNP levels increased similarly in both studies groups. The decrease in LVEF in the control group was significantly higher than in the spironolactone group (67.7 \pm 6.3 vs 53.6 \pm 6.8 mm). Spironolactone was found to provide significant protection of diastolic fraction.³² On the other hand, a recent experimental study on eplerenone did not confirm the protective effect in preventing doxorubicin-induced cardiotoxicity.¹²

Statins

Seicean et al (Table 1) studied women with breast cancer receiving anthracycline chemotherapy and found that statin use was associated with a lower risk of incident heart failure. However, the assessment of the effectiveness of statins was difficult because approximately 40% patients used other potentially cardioprotective medications (ACEIs and β -blockers) and had significantly less cardiovascular risk factors (family histories of cardiovascular disease and lower low-density lipoproteins).³³ Cardioprotective effect of statins may be associated with their significant pleiotropic

effects, such as antioxidative and anti-inflammatory properties. In the study of Acar et al (Table 1), atorvastatin was administered, in a dose 40 mg daily for six months, to patients who had a history of chemotherapy or radiotherapy without cardiovascular diseases, treated with adriamycin or idarubicin. Atorvastatin has been shown to reduce a decrease in left ventricular ejection fraction ($p < 0.0001$). Moreover, the mean increase in LVEDD and LVESD was significantly lower in the statin arm, compared to the control group ($p = 0.021$; $p < 0.001$, respectively).³⁴ Similar results were demonstrated by Chotenimitkhun et al (Table 1) in the oncological participants with hyperlipidemia and other cardiovascular risk factors, who received atorvastatin or simvastatin. A high statin dose (40–80 mg/day) was associated with a non-significant increase in LVEF compared to the placebo group, in which LVEF declined significantly.³⁵ Recent study by Calvillo-Argüelles et al has also confirmed cardioprotective effect in the group of women with breast cancer receiving trastuzumab-based therapy.³⁶

Ranolazine

Cappetta et al performed an experimental study with ranolazine and suggested that this drug may protect cardiomyocytes from doxorubicin-induced oxidative stress.³⁷ Other authors point out that the use of ranolazine may be beneficial in diastolic dysfunction and chemotherapeutic cardiotoxicity, due to its capacity to reduce late sodium current and cytosolic Na⁺, and consequently to counteract intracellular Ca²⁺ accumulation. On the other hand, concomitant use of ranolazine and doxorubicin can be limited because of potential interaction, associated with absorption and biotransformation.^{38–40}

Trimetazidine

Cardioprotective properties of trimetazidine (60 mg/day) were assessed in 61 patients with breast cancer treated with an anthracycline (Table 1). The results showed that trimetazidine, similarly to dexrazoxane, provided a cardioprotective effect. Its efficacy was associated with protection against subacute and chronic subclinical cardiotoxicity with no significant changes in diastolic function after one year of follow-up.⁴¹

Ivabradine

So far, there are no clinical trials concerning ivabradine as a cardioprotective agent for oncological patients, despite its hemodynamic and biochemical parameters. A case report, published by de Gregorio et al, reported full

restoration of left ventricular function, with no residual myocardial damage, after applying combination therapy with ivabradine, lisinopril and multivitamin supplementation. This finding supports the need for an experimental study on the potential therapeutic effect of ivabradine against doxorubicin-induced cardiotoxicity.^{42,43}

Coenzyme Q10

First studies showing the potential cardioprotective effect of coenzyme Q10 (CoQ10) were published in the previous century.^{44–46} Recently, Mustafa et al performed an experimental study on rats treated orally with a single dose of doxorubicin (10 mg/kg) - they observed that CoQ10 supplementation (200 mg/kg) improved the functional and structural integrity of the myocardium.⁴⁷

Pharmacogenetics

Genetic diversity can influence the functioning of various drugs. It may also affect the risk of developing drug-induced cardiotoxicity. The progress in pharmacogenetics can, therefore, increase the possibilities of avoiding this adverse effect. According to Canadian Pharmacogenomics Network for Drug Safety Clinical Practice Recommendations Group, three SNPs in three genes have been found to be associated with increased risk of anthracycline cardiotoxicity in pediatric population: RARG rs2229774 (retinoic acid receptor gamma), SLC28A3 rs7853758 (solute carrier family 28 member 3) and UGT1A6*4 (UDP glucuronosyltransferase family 1 member a6) rs17863783. Assessment of these polymorphisms was therefore recommended for pediatric patients undergoing doxorubicin or daunorubicin treatment. No such recommendation was eligible for adult patients due to the lack of studies on adult populations. One of such studies was recently published by Schneider et al who found rs28714259 polymorphism associated with increased risk of anthracycline cardiotoxicity. However, further studies are required to provide recommendations for the adult population.^{48,49}

Summary

Despite the large and an increasing scale of the problem of clinical oncological treatment in the form of cardiotoxicity, data from clinical trials carried out so far do not allow for the creation of clear recommendations regarding the use of cardiovascular drugs in the prevention of this complication. This is due to heterogeneous and small-sized populations of patients treated with various antitumor drugs that are

cardiotoxic in different dosing regimens. Additionally, the cardioprotective drugs used in clinical trials were administered in a wide range of doses. The main purpose of their application was to assess their effectiveness in the prevention of primary development of post-anthracycline cardiomyopathy and heart failure.

The most serious cardiological adverse effect of oncological treatment (epidemiology, clinical consequences) is cardiomyopathy, which may lead to heart failure. Current data suggests the usefulness in cardioprotection of only some cardiovascular drugs recommended for the treatment of heart failure. The most promising examples from the review include carvedilol and nebivolol, enalapril, candesartan and the combination of carvedilol and enalapril. Both β -blockers and RAA inhibitors prevent adverse remodeling, and their combination improves prognosis and reduces mortality. The advantage of β -blockers is that they correct the elevated heart rate (resulting from autonomic disorders caused by anthracyclines), which is an independent factor of morbidity and mortality. These cardiovascular drugs not only are effective in the prevention of left ventricular dysfunction, but also in other forms of cardiotoxicity (hypertension, arrhythmia, myocardial ischemia). Their use in patients without cardiovascular disease is not associated with the risk of serious adverse effects, especially if their dosage is gradual. Alternatively, in case of adverse reactions, statins might be considered. Besides, an important element of cardioprotection strategy in these patients should be the modification of lifestyle (eg, smoking, alcohol consumption, low physical activity) which can have a negative effect on cardioprotective drug efficacy.

Currently, the lack of recommendations concerning cardioprotection in oncological patients increases the risk of cardiotoxicity which may lead to serious consequences for health and life. The “2016 European Guidelines on cardiovascular disease prevention in clinical practice” have listed β -blockers, ACEIs, dexrazoxane, and statins as prophylactic agents to reduce chemotherapy-induced cardiotoxicity. Based on the clinical studies discussed in our review, the guidelines’ suggestions may be expanded/enhanced with:

1. introducing cardioprotective agents only in patients with subclinical heart injury (confirmed by increased troponin, decrease in global longitudinal strain: GLS, reduction of LVEF)
2. titrating the dose of the cardiovascular drug, starting from the lower dose and reaching the most optimal

dose for the patient; adverse drug reactions monitoring must be mandatory

3. monitoring myocardial damage with imaging technology (eg, ECHO, nuclear magnetic resonance, equilibrium radionuclide angiocardiology/multi-gated acquisition) and troponin level

The above suggestions relate to the primary prevention of chronic cardiotoxicity. Their effectiveness seems to us to be dependent on strict adherence to the principles of detecting and monitoring cardiotoxicity. Ongoing advance in cardiovascular diagnostics (biochemical markers, imaging technologies) gives tools to define new targets for assessing cardioprotection efficacy (NT-proBNP, troponin, GLS besides ejection fraction).

Disclosure

The authors report no conflicts of interest in this work.

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