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Heart failure and oncologic treatment

Srčno popuščanje in onkološko zdravljenje

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Abstract

Heart failure after oncological treatment is a hot topic in oncology as well as in cardiology and it demands quick diagnostic and therapeutic interventions. The most commonly used classification of myocardial damage is still type I (anthracycline-like) and type II (trastuzumab-like) myocardial injury. Radiotherapy is also a significant contributor to cardiotoxicity in onco-logic patients. The European Society of Cardiology has published guidelines regarding surveillance and follow up of such patients, the golden standard of imaging techniques being echocardiography. Other imaging techniques and laboratory modalities could be used but are not widely available. This year's recommendations of the European Society of Medical Oncology advise considering the use of cardioprotective medications before and during therapy in individuals with known cardiovascular risk factors. However, individual approach to every patient is of paramount importance.

Izvleček

Srčno popuščanje po onkološkem zdravljenju je vse bolj aktualna tema, ki zahteva hitro obravnavo ter čimprejšnje zdravljenje. K nastanku močno prispevajo bolnikovi predobstoječi dejavniki. Vedno najpogosteje uporabljamo delitev poškodb miokarda na tip I (predstavniki so antraciklini) in tip II (glavni predstavnik je trastuzumab), svojstvena entiteta pa je tudi obsevalno zdravljenje. Evropsko združenje za kardiologijo je objavilo priporočila za presejanje in sledenje onkoloških bolnikov. Glavna priporočena presejalna metoda pa je ehokardiografija. Uporaba ostalih slikovnih in laboratorijskih metod je odvisna od dostopnosti osnovne preiskave. Letošnja priporočila Evropskega združenja za internistično onkologijo prvič svetujejo uvajanje kardioprotektivnega zdravljenja pri ogroženi populaciji. Za doseganje optimalnih rezultatov zdravljenja pa je potrebna individualna obravnava vsakega bolnika.

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1 Introduction

In 2016, according to the Slovenian Cancer Registry, 15,072 patients were diagnosed with cancer (1). The development of the profession and the pharmaceutical industry brings new and more demanding drugs into everyday clinical practice; drugs with adverse effects and mechanisms of action that are often not yet fully

defined. However, the adverse effects of oncological treatment on the cardiovascular system are an increasingly recognizable complication. They are important especially because of the growing population of patients with curable cancer. After a successful oncological treatment, the life expectancy of these patients is long, so so consequences of oncological treatment can have a significant negative impact. Adverse effects of oncological treatment can be divided into early and late according to the time of onset. In analysing the latter, the European Society of Cardiology (ESC) identified nine categories of cardiovascular complications: myocardial dysfunction and heart failure, coronary heart disease, valvular disease, arrhythmias, arterial hypertension, thromboembolic disease, peripheral vascular disease, pulmonary hypertension, and pericardium-related complications (2). The heart failure syndrome is considered to be one of the most important complications of oncological treatment in cancer patients, as it significantly increases the morbidity and mortality rates of this group of patients.

In this review article, we want to present the mechanisms of heart failure following various forms of oncological treatment and present the possibilities of heart failure prevention and strategies for this treatment in oncological patients.

2 Mechanisms of heart failure in systemic cancer treatment and radiotherapy

Cardiotoxic drugs are divided by the type of myocardial damage they cause and according to how long-lasting it is. Type I damage is associated with cell death and consequently with irreversible myocardial damage. This type of damage is most commonly seen in anthracycline treatment. Type II damage, with trastuzumab as the main agent, is expected to be (at least partially) curable (2-4). In everyday clinical practice, however, the division into myocardial damage of types I and II is blurred, as patients are often treated with a combination of chemotherapeutics, either concurrently or sequentially, with myocardial toxicity of these drugs likely to be synergistic (5). The general risk factors for the onset of cardiotoxicity are summarized in Table 1. Patients with a familial predisposition to cardiovascular disease, pre-existing heart disease, and patients with an unhealthy lifestyle are the most susceptible to developing cardiotoxicity.

2.1 Type I myocardial injury

Type I myocardial injury is most often represented by an anthracycline cardiotoxicity model. There are several proposed mechanisms for the development of anthracycline cardiotoxicity. Anthracyclines bind to DNA, inhibit topoisomerase II-beta, leading to impairment of DNA repair mechanisms; they also impair protein synthesis and cause the release of free oxygen radicals. All of the listed effects can lead to cardiomyocyte apoptosis (5,7). Anthracycline treatment therefore leads to a loss of cardiomyocyte mass, which makes its effects irreversible. Risk factors associated with the development of anthracycline cardiotoxicity are: cumulative dose of anthracycline used, age below 18 years or over 65 years at the start of treatment, female sex, chronic kidney disease, any irradiation in the cardiac area, concomitant treatment with microtubule inhibitors, alkylating agents, immunotherapy or targeted therapy, and individual patient characteristics (certain genetic polymorphisms (8), arterial hypertension, pre-existing cardiovascular disease, diabetes, smoking, menopause, etc.) (2,5). Anthracycline cardiotoxicity can be acute, subacute, or late. Acute anthracycline cardiotoxicity is extremely rare and is clinically mostly manifested by changes in ECG changes, supraventricular arrhythmias, and transient left and/or right ventricular dysfunction. Subacute anthracycline cardiotoxicity typically presents within the first 12 months

Table 1: General factors that make patients more susceptible to developing cardiotoxicity (2,6). LV – left ventricle, PCI – percutaneous angioplasty, CABG – Coronary artery bypass grafting.

Demographic factors	Lifestyle factors	Current cardiological state	Previous cardiotoxic therapy
Age (paediatric population < 18 years, age over 65 years with anthracycline treatment and age over 50 years with Trastuzumab therapy).	Smoking.	Heart failure (regardless of LV ejection fraction).	Previous anthracycline treatments.
Family history of early cardiovascular disease (onset before age 50).	Obesity.	Asymptomatic LV dysfunction.	Previous mediastinal or chest wall irradiation.
Arterial hypertension.	Excessive alcohol consumption.	Elevated serum biomarker values before the start of oncological treatment.	
Diabetes.	Predominantly sedentary lifestyle without sufficient physical activity.	Coronary heart disease (prior myocardial infarction, angina pectoris, condition following PCI or CABG).	
Hypercholesterolemia.		Moderate or severe valve failure with hypertrophy or impaired LV function.	
		Hypertensive heart disease with LV hypertrophy.	
		Cardiomyopathies:	
		• cardiac sarcoidosis with myocardial involvement,	
		• significant cardiac arrhythmias (e.g., atrial fibrillation, ventricular tachycardias).	

after initiation of anthracycline therapy, whereas late anthracycline cardiotoxicity manifests later. Clinically, it usually manifests as heart failure syndrome a few years after the end of treatment. There is no uniform definition for late anthracycline cardiotoxicity in the literature. Some authors identify it as early as in the first year following treatment (9), some set the median at 7 years after treatment (2,10), and cardiotoxicity 20 years after treatment has also been described (10). If heart failure is detected early enough, progression can be relatively effectively slowed with appropriate treatment. However, in patients with a late form of anthracycline cardiotoxicity and an advanced heart failure, the response to treatment of heart failure is generally poor, which is why non-pharmacological forms of treatment for heart failure should be considered (11). Cumulative doses of anthracyclines are associated with a higher risk of heart failure. Significant risk (probability of 5% or more) of developing heart failure after anthracycline treatment occurs with a cumulative dose of doxorubicin above 400 mg/m^2, epirubicin above 900 mg/m^2, idarubicin above 150 mg/m^2 and daunorubicin above 800 mg/m^2 (2).

Among other classic chemotherapeutics, cyclophosphamide, ifosfamide, paclitaxel, docetaxel, and cisplatin also cause heart failure, but all in much lower percentages than anthracyclines (2,5).

2.2 Type II myocardial injury

Trastuzumab is the most studied cardiotoxicity-related monoclonal antibody that binds to human epidermal growth factor receptor 2 (anti-HER2) and is used mostly, but not exclusively, in the treatment of breast cancer that has an overexpressed HER2 receptor. Other anti-HER2 drugs currently in use in Slovenia are lapatinib (a tyrosine kinase inhibitor that also binds to the HER2 receptor), pertuzumab (an anti-HER2 antibody) and T-DM1 (an antibody-drug conjugate in which the cytotoxic substance emtansin (DM1) is bound to trastuzumab). HER2 receptors are also expressed on cardiomyocytes (5). The generally accepted putative mechanism of action of anti-HER2 drugs are the changes in the structure and function of

Table 2: Diagnostic methods for the detection of heart failure (summarized after (2) and (6)). LP - left ventricle, GLS - global longitudinal strain, LVEF - left ventricular ejection fraction, BNP - B-type natriuretic peptide, NT-proBNP - N-terminal segment of B-type natriuretic peptide, ACE - angiotensin-converting enzyme.

Diagnostic method	Current diagnostic criteria
Echocardiography (3D estimate of LV ejection fraction, 2D estimate of LV ejection fraction according to Simpson, GLS)	LVEF: decrease of 10 % below the lower limit of normal signifies cardiotoxicity. GLS: a relative decrease of > 12 % from the basal measurement indicates the possibility of cardiotoxicity or an absolute decrease of 5 %.
Nuclear cardiac imaging (MUGA-multigated radionuclide angiography)	A reduction of 10% of the LV ejection fraction to a value below 50 % signifies cardiotoxicity.
Magnetic resonance imaging of the heart	It is mostly a supplementary method when other techniques are not conclusive, or to confirm LV dysfunction at borderline pathological LVEF.
Serum biomarkers (troponin I, high-sensitivity troponin I, BNP, NT-proBNP)	An increase in troponin might help identify patients for whom the addition of an ACE inhibitor would be beneficial during treatment with anthracyclines. Routine use of BNP and NT-proBNP in the monitoring of high-risk patients requires further research.

contractile proteins and mitochondria in the myocardium, which do not lead to cell death but to damage of the contractile elements of cardiomyocytes. This explains the reversibility of trastuzumab cardiotoxicity (2). Clinically, the cardiotoxicity of trastuzumab is mostly manifested as an acute decrease in left ventricular ejection fraction (LVEF) or as symptomatic heart failure, which usually resolves upon discontinuation of treatment and initiation of supportive cardioprotective therapy (2). Trastuzumab treatment leads to heart failure syndrome in 1.7–4.1%, while asymptomatic left ventricular dysfunction is more common (7.1–18.6%) (12). In a 2012 Cochrane meta-analysis, the relative risk of heart failure after trastuzumab treatment was 1.8% when analysing nearly 12,000 women with HER2-positive breast cancer (13). The incidence of cardiotoxicity may further increase in patients treated concomitantly with anthracyclines (2,5,13). As concomitant use of anthracyclines and trastuzumab is not recommended, the drugs are used sequentially in the treatment of breast cancer (14). The cardiotoxicity of other anti-HER2 drugs is similar to that of trastuzumab (15-17).

Vascular endothelial growth factor (VEGF) inhibitors are also a group of drugs that can cause type II myocardial damage, which can lead to heart failure. The mechanism of cardiotoxicity is complex, as these inhibit multiple signalling pathways in the cell simultaneously. The myocardium is affected by both anti-VEGF antibodies (bevacizumab, ramucirumab) and tyrosine kinase inhibitors (2). In a meta-analysis of more than 10,000 patients, the risk of developing heart failure was 2.69-fold higher compared to control groups in which the patients were not treated with VEGF inhibitors. The meta-analysis included treatment with the following tyrosine kinase inhibitors: sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib and regorafenib (18). The prognosis of the outcome and the dynamics of the effects of cardiotoxicity of VEGF inhibitors are difficult to assess, as these drugs are usually used in the metastatic setting. Therefore, most patients die before the late effects of treatment can develop (2).

2.3 Myocardial damage after radiation therapy

The harmful effects of radiotherapy on the heart have been known for a long time (5). Heart failure after irradiation can manifest itself acutely as myocarditis, but more often occurs after a long period of time (several years, even decades (19)). Irradiation can cause endothelial, microvascular, and macrovascular injury, valve injuries and damage, and pericarditis. Heart failure after radiotherapy is caused by interstitial myocardial fibrosis (19), and the clinical manifestation is determined by the amount and distribution of the resulting fibrosis (19,20). Myocardial fibrosis usually develops at an irradiation dose above 30 Gy (19). The presence of general risk factors for cardiovascular disease and possible treatment with cardiotoxic drugs further increase the likelihood of heart failure in patients who have also been irradiated as a part of cancer treatment (2,5). Adverse effects of irradiation are most commonly seen in patients treated for early-stage breast cancer or in patients after treatment for lymphoma in the mediastinum (19), in whom the heart cannot be completely removed from the irradiated field. It is important to know that heart failure can also occur decades after mediastinal irradiation (21).

2.4 Newer drugs and immunotherapy

Heart failure syndrome can occur after ischemic heart disease that with various chemotherapeutic agents (fluoropyrimidines, platinum derivatives) as well as during treatment with target drugs (VEGF inhibitors), after radiotherapy or after treatment with hormonal drugs, e.g., aromatase inhibitors used to treat breast

cancer patients for several years (2,22). Immunotherapy is currently hot topic in oncology, especially treatment with immune checkpoint inhibitors, which causes otherwise rare adverse effects on the heart, as they occur in less than 1 % (23)). Immune checkpoint inhibitors act by a mechanism boosting the immune system response, which then attacks cancer, and occasionally its own cells. So far, we have found descriptions in the literature of some cases of myocarditis (also of the fulminant course), which occurred as part of immunotherapy (24-26). The long-term effects of immunotherapy on the cardiovascular system are not yet known, as the drugs in question are newer and long-term experience is yet to be obtained.

3 Possibilities of preventing heart failure in oncological patients

3.1 General screening

For each patient treated with one of the possible cardiotoxic drugs, it is necessary to first determine the basic risk factors for the development of cardiotoxicity (Table 1) and try to influence those factors that can be regulated by non-pharmacological measures (promotion of a healthy lifestyle, regular aerobic exercise, smoking cessation, and abstinence from alcoholic beverages) (2). Further screening methods are laboratory (determination of natriuretic peptides, determination of troponin I or T) and imaging (echocardiography, magnetic resonance imaging of the heart, nuclear cardiac imaging). The recommendations of the European Society of Cardiology leave the choice of modalities upon local expertise and availability (poorer availability of magnetic resonance imaging nuclear cardiac imaging), while recommending the use of the same algorithm in individual patient monitoring (2). Several different scoring predictive models of cardiotoxicity have also been published, but they have not yet been prospectively validated, so they are not widely used in everyday practice (2,5). The proposed diagnostic methods are presented in Table 2. At the beginning of 2020, the recommendations of the European Society for Medical Oncology (ESMO) for the monitoring and cardiac treatment of oncological patients were also published (6).

3.1.1 Echocardiography

Echocardiography is recommended as the main screening method. Whenever possible, 3D assessment of the left ventricular ejection fraction is recommended, but if 3D LVEF assessment is not possible, the guidelines still recommend 2D left ventricular ejection fraction estimation using the Simpson method (2,4,6). Cardiotoxicity is defined as a 10% decrease in the LVEF below the lower normal limit (4). If signs of cardiotoxicity are observed during treatment with cardiotoxic chemotherapeutics, ultrasound examination of the heart should be repeated after 2-3 weeks to confirm cardiotoxicity (4).

Due to the interobserver variability of the method, it is recommended that the examination is performed by the same examiner whenever possible (4). The use of contrast echocardiography should be considered when visibility is poor. Stress echocardiography discover additional patients with a high risk of developing cardiotoxicity, although the data is currently insufficient to support the routine use of this test in screening patients prior to the start of the oncological treatment (2). Measurements of myocardial deformity are highly recommended, as GLS (global longitudinal strain) assessment is used to determine impaired myocardial systolic function before the global parameters of myocardial systolic function decrease (LVEF is most commonly used) (27). Cardiotoxicity occurs when the GLS is reduced by 12% or more from the baseline value, or when there is an absolute reduction of 5 points or more (6). The GLS is expected to have better reproducibility,

with smaller variability deviations than the classic LVEF measurements (6). Diastolic dysfunction is commonly identified in cancer patients both before and during treatment. To date, there is no evidence to support changes of oncological treatment plan solely on the basis of the presence of diastolic dysfunction (2).

3.1.1.2 Nuclear cardiac imaging and magnetic resonance imaging (MRI)

Nuclear cardiac imaging is a well-reproducible method, but it exposes the patient to irradiation and provides much less information about the morphology and structure of the heart than echocardiography (5). A heart MRI is an accurate imaging method that provides a lot of information about the structure and function of the myocardium and is most often used as a complementary method to clarify the cause of left ventricular dysfunction (28). It is also useful for assessing the pericardium, especially in patients who have had chest irradiation. The use of Gadolinium contrast medium allows for the most accurate assessment of myocardial fibrosis of all other imaging modalities (2,28). However, due to the procedure of image capture and mostly qualitative analysis, diffuse myocardial fibrosis can be missed after treatment with anthracyclines (28).

3.1.1.3 Determination of serum biomarkers of myocardial damage and heart failure

Determination of serum biomarkers of myocardial damage and heart failure probably makes sense in early detection of cardiotoxicity, but based solely on elevated values without other evidence; without other evidence of myocardial dysfunction, discontinuation or modification of oncological treatment should not be considered (2,6). Further research is necessary to determine the optimal timeframe for the identification of these biomarkers and their reference values, that would guide further actions and predict patient outcome (2,5,6). Individual recommendations for the determination of serum markers according to the used method of treatment are presented below.

The ESC recommendations conclude that the choice of methods and frequency of cardiotoxicity monitoring during/after oncological treatment should be tailored to each patient as well as the accessibility and capabilities in the treatment environment (2).

3.2 Screening according to the type of oncological treatment

3.2.1 Anthracyclines

A baseline assessment of cardiac function is recommended for all patients receiving treatment with anthracyclines (2,4,6,29). If systolic function is reduced (LVEF below 40%) or if significant valve pathology is present, consultation with a cardiologist or consideration of changing the therapeutic regimen (discontinuation of anthracyclines, replacement with another, non-cardiotoxic drug) is required (29). For treatment with higher doses of anthracyclines, cardiac function (echocardiography, including 3D assessment of LVEF and GLS) should be re-evaluated (4) as soon as a cumulative dose of doxorubicin 250 mg/m^2 or an equivalent dose of a different anthracycline is reached, and then before each additional 50 mg/m^2 increment (2,4,6,30). Ultrasound monitoring is also recommended 12 and 18 months from the start of anthracycline treatment, regardless of the cumulative dose received (6,29,30). Following the completion of anthracycline therapy, the new ESMO recommendations state that a patient should be monitored by ultrasound at 6–12 months and for 2 years after completion of treatment if there are no symptoms (6).

In patients receiving anthracyclines, it is also recommended to perform a baseline determination of serum biomarkers for heart muscle damage and heart failure – the high-sensitivity troponin I or T and natriuretic peptides (2,6). Measurements of troponin and natriuretic peptides levels

can be repeated with each anthracycline cycle (6). An early increase in troponin I value during anthracycline treatment is in 34% connected with the development of diastolic dysfunction (31). Troponin is useful in this population especially due to its high negative predictive value. This means that patients who do not have an increased troponin values during treatment have only a minimum risk of developing early cardiotoxicity (32). However, it has not yet been demonstrated that determining troponin values a regular basis prevents or reduces the number of cardiac events due to late cardiotoxicity after anthracycline treatment (2). The ESC recommendations conclude that an increase in any of the serum biomarkers of heart muscle damage and heart failure may identify patients who are more prone to developing heart failure and are likely to need more careful monitoring (2). The new ESMO recommendations advise the introduction of cardioprotective treatment based on the observed increase in troponin (6).

In study of Cardinal et collegues, an analysis of over 2,500 patients showed that most cases of anthracycline cardiotoxicity were asymptomatic left ventricular dysfunction that occurred within the first year after treatment (9). This underlines the need of regular screening of all patients after completion of anthracycline treatment. The same working group also found that with anthracycline cardiotoxicity, early introduction of heart failure therapy (in their case, enalapril and carvedilol) leads to a significantly more effective treatment of heart failure, which further supports regular ultrasound monitoring of anthracycline-treated patients (11).

3.2.2 Trastuzumab

Analogous to antracyclin treatment, baseline ultrasound assessment of cardiac function is recommended prior trastuzumab therapy. During treatment with trastuzumab, in asymptomatic patients, ultrasound assessment of cardiac function is recommended for every 3 months of treatment (2,4,6,29). If the ultrasound result is normal, ultrasound monitoring is recommended for another 6–12 months and 2 years after the end of treatment (4,6) or for another 12 and 18 months from the start of treatment (29,30). Troponin level

Table 3: Summary of patient monitoring recommendations (2,4,6,24,25). 1 – in the treatment of metastatic disease, a baseline assessment is recommended and then further assessments according to the course of the disease and the clinical picture. * – if possible, a 3D assessment is recommended; if not, 2D. ** – monitoring may also be performed by isotope ventriculography, but echocardiography is recommended. *** – the criterion previously met is taken into account. VEGF – vascular endothelial growth factor, GLS – global longitudinal strain.

Method of treatment	Recommendations
Anthracycline treatments[1]	Baseline assessment by echocardiography, including 3D* assessment of LVEF, GLS and troponin I (or nuclear cardiac imaging**). GLS echocardiography at achieved cumulative doxorubicin dose at 250 mg/m^2, followed by additional 50 mg/m^2 increments. Echocardiography 6–12 months and 2 years from the start of treatment.
Trastuzumab treatment[1]	Baseline assessment by echocardiography, including 3D* assessment of LVEF, GLS and troponin I Echocardiography every 3 months of treatment, including GLS and determination of troponin I. Echocardiography for another 12 and 18 months from the start of treatment.
VEGF inhibitor treatment	Baseline assessment by echocardiography. In high-risk patients, reassessment after 2–4 weeks of treatment. Echocardiography every 6 months.
Radiotherapy treatment	If the patient has also been treated with other cardiotoxic substances, see recommendations: start of screening 5 years after the end of treatment or after 30 years of age***

determination on a regular basis is also recommended in patients with high risk for onset of cardiotoxicity (2). Elevated troponin levels have been associated with the development of acute cardiotoxicity and the development of persistent myocardial damage during adjuvant therapy with trastuzumab (33). In a study by Saway et al., the high-sensitivity troponin I and GLS, determined after anthracycline treatment and before the start of trastuzumab treatment, were shown to be predictors of trastuzumab-related cardiotoxicity with 93% sensitivity and 91% negative predictive value (34).

3.2.3 VEGF inhibitors

The exact time frame for monitoring cardiac function in VEGF inhibitor therapy has not yet been established. In any case, it is recommended to assess cardiac function at baseline and then reassess the condition in high-risk patients 2–4 weeks after starting treatment with sunitinib, sorafenib and pazopanib and to monitor their condition every 6 months (2). Continuous blood pressure measurements (arterial hypertension is one of the most common side effects of this treatment) and adjustments of antihypertensive therapy in the light of the management of the patient's cardiovascular risk factors are also recommended (6).

3.2.4 Radiotherapy

The main options for preventing myocardial damage in radiotherapy treatment are improved irradiation techniques that are more accurate and more fractionated with lower doses and less damage to surrounding tissue (19). After radiotherapy, screening recommendations differ. In most cases, it is recommended to start screening 5 years after the end of treatment or after the age of 30, depends which criteria is met earlier (19). Thereafter, monitoring is continued every 3–5 years (6). However, these are often patients who have been treated with anthracyclines or trastuzumab at the same time, so in this case, we follow the guidelines that apply to follow-up with these drugs. Screening methods without excessive irradiation (for example ultrasound) and are non-invasive are recommended in the first place (19).

3.2.5 Immunotherapy

Recommendations for follow-up of patients treated with immunotherapy (particularly immune checkpoint inhibitors) are based on expert consensus with data from retrospective analyses or observational prospective studies. If a patient develops symptoms of cardiotoxicity during treatment, a cardiologist should be consulted immediately, serum biomarkers need to be determined, and echocardiography or magnetic resonance imaging of the heart performed searching for miocarditis. Regular screening of asymptomatic patients or long-term cardiac monitoring of patients is not required. Only monitoring of patients with observed cardiotoxicity further is advised (6).

The recommendations for the cardiac follow-up of patients during and after oncological treatment are summarized in Table 3.

4 Prevention and treatment of heart failure caused by oncological treatment

4.1 Prevention of heart failure in oncological patients

Prophylactic use of cardioprotective drugs (ACE inhibitors, sartans, beta blockers and mineralocorticoid antagonists) in all patients is not yet widely accepted due to inconsistent data in the literature regarding the effectiveness of this approach. Cochran's meta-analysis (13), which included randomized trials of cardioprotective drugs in cancer patients published so far, showed that none of the drugs tested had statistically significant cardiac protection. In two smaller studies of 50 patients, carvedilol (35) and nebivolol (36) were

shown to be effective in preventing LVEF lowering, and in a retrospective analysis of 315 patients, patients taking beta-blockers during oncology treatment had lower incidence of heart failure with both anthracyclines and trastuzumab (37). A prospective, randomized OVERCOME study demonstrated a lower incidence of heart failure and LVEF reduction in the preventive use of the combination of enalapril and carvedilol in patients treated with anthracyclines (38). Two studies on positive effects on sartan valsartan (39) and telmisartan (40) have also been published. They have shown that sartans (valsartan) can successfully prevent a transient increase in LV end-diastolic diameter and changes in the QTc interval in the ECG (39) and telmisartan can prevent a decrease in GLS (40). A study of 83 breast cancer patients, treated with anthracyclines, further showed that prophylactic use of spironolactone successfully prevented the development of both systolic and diastolic myocardial dysfunction (41). In patients who tested positive for troponin during anthracycline treatment, taking an ACE inhibitor has been shown to significantly reduce LVEF decline and the likelihood of heart failure (42). However, an observational retrospective analysis of approximately 200 breast cancer patients receiving anthracyclines showed that patients were less likely to be hospitalized for symptomatic heart failure if they received statins continuously than those who did not receive statins or did not take them continuously (43). Prospective randomized research on the cardioprotective role of statins is currently underway.

Based on these data, ESC recommendations advise consideration on initiating cardioprotective treatment in patients with a positive troponin I value (2). However, the ESMO guidelines advise the introduction of cardioprotective drugs (ACE inhibitors, sartans and beta-blockers) before starting treatment in patients with known risk factors for cardiotoxicity when they are to be treated with cardiotoxic drugs (6). Dexrazoxane is recommended as a cardioprotective drug only in the treatment of metastatic breast cancer if the 300 mg/m^2 maximum cumulative dose of doxorubicin has already been reached (6,29).

The ESMO guidelines recommend the introduction of cardioprotective drugs even in asymptomatic patients with anthracyclines who have a fall in LVEF of more than 10% from baseline to 50%, or a reduction in LVEF of 40-50%. They also recommend the introduction of drugs in asymptomatic patients treated with trastuzumab and a fall in LVEF of more than 10% from baseline or a reduction in LVEF of 40-50%. A new development in ESMO recommendations compared to the ESC guidelines is the recommendation to introduce cardioprotective therapy in asymptomatic patients with normal LVEF, regardless of the type of cardiotoxic drugs and a reduction in GLS (absolute reduction of 5% or more, or relative reduction of 12% or more). ESMO recommendations also recommend the introduction of cardioprotective therapy in patients treated with anthracyclines who develop elevated troponin levels during treatment (with the simultaneous exclusion of ischemic heart disease) (6).

There are currently no studies or recommendations on cardioprotective treatment with immunotherapy.

4.2 Treatment of heart failure in oncological patients

If a cancer patient develops heart failure syndrome, a timely definitive diagnosis of the causes of heart failure and the introduction of cardioprotective drugs according to current ESC recommendations are required (44).

In cancer patients, the classic causes of heart failure (ischemic heart disease, valvular disease, heart failure due to hypertension and cardiomyopathy) should also be considered when diagnosing the aetiology of heart failure. In some cases (e.g.,

by myocardial revascularization, valve repair/replacement, regulation of blood pressure), we can significantly influence the course and outcome of treatment of heart failure (44). Toxic cardiomyopathy associated with oncological treatment is usually a diagnosis made when all other, more common causes of heart failure have been ruled out. The definitive diagnosis of toxic cardiomyopathy is otherwise histological. However, in practice, myocardial biopsy is performed only in cases when non-invasive tests cannot prove the diagnosis reliably enough, or when histological examination could significantly change further oncological treatment or treatment of heart failure.

Regardless of the aetiology of heart failure, cardioprotective drugs should be introduced as soon as the patient is diagnosed with heart failure (clinical manifestation, elevated natriuretic peptides, signs of heart failure on echocardiography). There is growing evidence that early introduction is associated with greater success in the treatment of toxic cardiomyopathy (45). Patients with toxic cardiomyopathy resulting from oncological treatment have the same principles of treatment for heart failure as the general population. In patients who develop a heart failure phenotype with reduced left ventricular ejection fraction (LVEF < 40 %; i.e., HFrEF); treatment is based on a combination of renin-angiotensin-aldosterone axis inhibition (with ACE inhibitors, sartans, beta-blockers and mineralocorticoid antagonists) and neurohumoral modulation with neprilysin inhibitors (which replace ACE inhibitors or sartans). The prognostic role of this treatment in patients with a heart failure phenotype with preserved ejection fraction (LVEF > 50 %; i.e., HFpEF) is less clear. To date, there has been no clear evidence to support the use of cardioprotective drugs in this patient population. Regardless of the phenotype of heart failure in symptomatic patients with heart failure, we also use symptomatic drugs (diuretics, nitrates, digoxin), which effectively reduce the symptoms and signs of heart failure, but do not affect the outcome of the disease.

The duration of treatment for heart failure in oncological patients is not clearly defined. Depending on the type and the duration of treatment, we decide according to the patient's initial laboratory and imaging results, according to their trends of improvement or deterioration, and according to the patient's well-being. With complete restitution of cardiac function, a reduction or even discontinuation of cardioprotective drugs (the latter is rarely chosen) can be considered with persistent normal laboratory and imaging results. In the event of a worsening heart failure despite optimal drug treatment, other measures (e.g., a pacemaker) may be considered in this patient population as well. However, levosimendan infusion should be applied patients with advanced heart failure (44). An active malignant disease or a malignant disease in the last 5 years is the absolute contraindication for performing a heart transplantation or a mechanical support of blood circulation, which is why oncological patients are generally not suitable for this type of treatment. However, if more than 5 years have passed since the end of treatment and the patients are in stable remission, heart transplants or mechanical circulatory support are also possible for these patients. The final opinion on this in our country is always given by the Council for Transplantation of the Advanced Heart Failure and Transplantation Program.

5 Conclusion

Heart failure is an important consequence of oncological treatment. Timely diagnosis, early treatment and referral to skilled cardiologic center can significantly improve the outcome in patients who develop heart failure after otherwise successful oncological treatment. Due to the growing number of cardio-oncological patients, they are establishing focused car-

dio-oncology centres around the world that provide a more standardized treatment of these patients. We do not have such a treatment model yet. Such timely and high-quality treatment of cardiac-oncological patients is ensured through good cooperation between the oncologist, general practitioner and cardiologist.

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