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Chemotherapy-induced cardiomyopathy

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Abstract Cardiomyopathy is an adverse outcome of antineoplastic drug therapy that has become increasingly relevant in the management of cancer survivors. As the efficacy of anticancer treatments has improved, long-term outcomes are altered by the development of cardiotoxicity, which may be associated with an even worse prognosis than that of the underlying malignancy. From the research into mechanisms, prevention, and treatment, the specialized field of cardio-oncology has evolved, but the recognition and appropriate management of these patients is important for the general internist and general cardiologist as well. Although antineoplastic chemotherapy can cause multiple forms of cardiotoxicity, including arrhythmia, pericardial disease, valvular dysfunction, and myocardial ischemia, in this review we will focus on chemotherapeutic agents associated with cardiomyopathies, from the anthracyclines to newer, the so-called targeted agents such as tyrosine kinase inhibitors. We also review the diagnostic modalities for chemotherapy-induced cardiomyopathy as well as the prevention and treatment strategies which may prolong the lives of those suffering from cancer.

Keywords Chemotherapy · Cardiomyopathy · Heart failure · Cancer · Cardio-oncology

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Introduction

The efficacy of chemotherapeutic agents has improved prognosis for cancer patients, yet chemotherapy-induced cardiomyopathy remains an important adverse outcome of treatment. Cancer chemotherapy drugs can cause multiple cardiovascular problems, including ventricular contractile dysfunction, pericarditis, hypertension, arrhythmias, and thromboembolism. Since left ventricular contractile dysfunction and cardiomyopathy are the most commonly encountered adverse cardiovascular effects of cancer chemotherapy, we will focus on this aspect of cardiotoxicity in this review. There are no consensus guidelines regarding prevention, monitoring, or treatment of patients at risk for chemotherapy-induced cardiomyopathy, and patients with cancer are often excluded from large heart failure trials. There are, however, multiple small retrospective cohort and randomized control trials. In this review, we aim to summarize the chemotherapeutic agents associated with cardiomyopathies as well as diagnostics, prevention, and treatment strategies.

Chemotherapeutic agents

Anthracyclines

Anthracyclines are a class of anti-neoplastic medications widely used in treatment of many malignancies. The cardiotoxic effects of doxorubicin were described decades ago. Initial literature focused on risk factors; a retrospective cohort study of 4018 patients published in 1979 identified increasing age and cumulative dose as major determinants of cardiac toxicity [1]. The incidence was estimated at 2 % with a mortality rate of 28–60 %;

however, these estimates are from an era when standard treatment of heart failure was limited to digoxin and diuretics [1, 2]. In a more recent retrospective analysis of 630 patients in three clinical trials, the dose-dependent nature of doxorubicin-induced heart failure (HF) was confirmed [3]. In this study, the estimated incidence of cardiac toxicity was much higher than previously reported (5 % at cumulative dose 400 mg/m^2, 26 % at 550 mg/m^2 and 48 % at 700 mg/m^2) [3]. This study also reported HF developing at a much lower dose (<300 mg/m^2) in 2 % of patients [3]. For this reason, the recommended cumulative dose is limited to 450–500 mg/m^2. However, in the era of combination chemotherapy, often administered in conjunction with potentially cardiotoxic biological agents such as trastuzumab, or with thoracic radiation therapy, there is no dose of anthracycline that can be assumed to be categorically safe.

The mechanism of anthracycline-induced cardiomyopathy has been well studied, and of the many mechanisms proposed, free radical-mediated oxidative damage to the cardiac myocyte, with membrane lipid peroxidation and mitochondrial dysfunction, is most widely accepted [4]. The time course of development of heart failure varies from an acute life-threatening myopericarditis to an early-onset (<1 year) or late-onset (>1 year) chronic progressive cardiomyopathy. The late-onset progressive cardiomyopathy can occur 10–30 years after exposure. Both chronic forms tend to be irreversible and are associated with ultrastructural changes in the cardiac myocytes [5]. This type of irreversible cardiotoxicity, which by definition is associated with both myocyte dysfunction and injury, is referred to as Type I chemotherapy-related cardiac dysfunction (CRCD).

Several attempts have been made to reduce the cardiotoxicity of anthracyclines without compromising antitumor efficacy. Altering dosing schedules, substituting continuous infusion for bolus administration, decreases the risk of clinical cardiotoxicity but is much less practical [6]. Epirubicin and idarubicin, like doxorubicin, are associated with a dose-dependent risk of cardiomyopathy (0.9–3.3 and 5–18 %, respectively) [7]. In a Cochrane meta-analysis, epirubicin was associated with a nonsignificant lower relative risk (RR 0.36) of clinical heart failure compared with doxorubicin at equivalent anti-neoplastic doses [8]. Liposomal-encapsulated doxorubicin has a significantly lower risk of clinical heart failure compared with conventional doxorubicin (RR 0.20), although there has been lingering concern over the possibility that reduced cardiotoxicity may come at the price of reduced antineoplastic activity [8]. It is approved in the USA for treatment of multiple myeloma and progressive or recurrent ovarian cancer. Pegylated liposomal doxorubicin has similar efficacy as doxorubicin with reduced cardiotoxicity in metastatic breast cancer and is approved in Europe for this indication [9].

Monoclonal antibodies

Trastuzumab is a monoclonal antibody to human epidermal growth factor receptor type 2 (HER-2/neu), one of a family of receptor tyrosine kinases that regulates cell growth and survival [10], which has been associated with a cardiomyopathy that is usually reversible. Twenty to thirty percent of invasive breast cancers overexpress or have mutations in HER-2/neu that allow homodimerization resulting in unregulated receptor tyrosine kinase activity and increased cell proliferation and survival [10]. Patients with HER-2-positive breast cancer suffer a worse prognosis and increased rate of recurrence [11]. As such, trastuzumab is an important adjuvant agent for patients with HER-2/neu-positive breast cancer.

In early trials, cardiac toxicity was recognized as the most common clinically significant adverse effect of trastuzumab [12]. The incidence of trastuzumab-induced cardiac dysfunction is estimated at 3 % when given alone, 5 % when given after anthracyclines, and 27 % when given concurrently with anthracyclines and is mostly New York Heart Association (NYHA) class III or IV HF [13]. What is often overlooked when interpreting the results of such studies is that "cardiac dysfunction," which is more precisely referred to as "left ventricular contractile dysfunction," can be associated with symptoms (such as effort intolerance, dyspnea, and edema) in which case the clinical syndrome of "heart failure" is said to exist. However, in many studies of cardiac dysfunction, whether caused by cancer chemotherapy agents or other factors, there exists a (sometimes larger) pool of patients with asymptomatic left ventricular contractile dysfunction. Patients with left ventricular dysfunction and heart failure have a much worse prognosis (often worse than that of the underlying cancer) than do those with asymptomatic left ventricular contractile dysfunction. In a more recent meta-analysis of eight studies and over eleven thousand patients, the risk of heart failure was 2.5 % in trastuzumab-containing regimens compared to 0.4 % in nontrastuzumab-containing regimens (RR 5.11) [14]. Age (≥50) and lower baseline left ventricular ejection fraction (LVEF) (≤55 %) are associated with increased risk [15]. Patients with traditional cardiac risk factors (hypertension, smoking, diabetes etc.) are also at increased risk of toxicity [13, 16].

The nature of trastuzumab-induced cardiotoxicity is distinctly different from that of doxorubicin and is referred to as Type II CRCD, which by definition is associated with myocyte dysfunction but not with irreversible injury. Ultrastructural changes seen on myocardial biopsy of patients treated with anthracyclines are absent on biopsy of

patients treated with trastuzumab [17, 18]. The HER2 (ErbB2) molecule is found on the extracellular surface of cardiac myocytes. When neuregulin 1-β binds the ErbB2 molecule, it activates a pathway that promotes cellular hypertrophy, protein synthesis, and cell survival; by blocking this pathway, the anti-HER-2 monoclonal antibodies cause damage to cardiac myocytes by abrogating the signaling that mediates activation of repair pathways, response to cellular stress and injury (including that caused by prior or concomitant anthracycline exposure), and anti-apoptosis [19]. This is the most likely explanation for the fact that cardiotoxicity of trastuzumab is much more frequent the sooner it is administered after completion of anthracycline therapy.

The reversibility of Type II CRCD distinguishes this form of cardiotoxicity from Type I CRCD. Several studies have shown that cardiomyopathy secondary to trastuzumab is reversible, with or without standard heart failure regimens [17, 20, 21]. While most patients will have resolution of LVEF and clinical heart failure, the cardiomyopathy can rarely be fatal. In a study of 38 patients with suspected trastuzumab-induced cardiotoxicity, 20 with clinical HF, LVEF improved in all patients who discontinued trastuzumab with a mean recovery time of 1.5 months, with recovery occurring spontaneously in 16 % and with initiation of heart failure treatment in 84 % [17]. Further, it may be safe to resume trastuzumab therapy in patients with an asymptomatic decline in LVEF, which resolves after 4 weeks of holding the medication [22].

It should be noted that overlap exists between the two classes of cardiotoxicity to the extent, for example, that early (but not late) anthracycline-induced cardiotoxicity is often reversible and, in some cases (particularly with prior anthracycline exposure), trastuzumab-induced left ventricular dysfunction fails to respond to withholding of trastuzumab. The distinction between Type I versus Type II cardiotoxicity is made further ambiguous in the setting of combination chemotherapy, in which multiple antineoplastic drugs, including both cytotoxic and targeted agents, are administered concurrently. Under such circumstances, a drug such as trastuzumab that is thought to induce reversible cardiomyocyte dysfunction may actually cause irreversible damage when administered concomitantly with, or soon after anthracycline therapy. In other words, while the initial damage to the cardiomyocyte-induced by exposure to an anthracycline may be to a limited extent survivable and repairable, when followed by a second hit in the form of trastuzumab (which interferes with survival and hypertrophic signaling), permanent damage and/or cell death may ensue.

Bevacizumab is a monoclonal antibody inhibiting vascular endothelial growth factor (VEGF) and is approved for the treatment of specific types of colon, lung, kidney, and brain cancer. Approval for breast cancer treatment was revoked in 2014 due to an unfavorable risk–benefit ratio. Among the risks is an increased incidence (1.6 %) and relative risk (4.74) of heart failure [23].

Alkylating agents

Alkylating agents take advantage of rapid proliferation of cancer cells by adding alkyl groups to DNA and, in the case of bifunctional alkylating agents, cross-linking the two strands, thereby preventing replication. Cyclophosphamide is an alkylating agent used in the treatment of autoimmune conditions and many cancers including lymphoma, leukemia, and breast cancer. Like anthracyclines, cyclophosphamide causes a dose-dependent reduction in LVEF and is limited by an acute (days to weeks) cardiomyopathy [24–27]. The incidence of high-dose (180 mg/kg over 4 days) cyclophosphamide-induced congestive heart failure has been reported as 28 % [26]. Another study showed that 3 % of patients who received $\leq$1.55 g/m^2/day over 4 days compared with 25 % of patients who received doses $>$1.55 g/m^2/day experienced cardiotoxicity (Goldberg, Mark). Autopsy of patients with cyclophosphamide-induced cardiotoxicity shows hemorrhagic myocardial necrosis with interstitial edema, hemorrhage, and fibrin deposition; however, the exact mechanism of cyclophosphamide-induced cardiomyopathy is not agreed upon [24]. Like anthracyclines, free oxygen radicals are thought to play a role [28, 29].

Ifosfamide is an alkylating nitrogen mustard used for treatment of lymphomas, sarcomas, and testicular, breast, and lung carcinoma [30]. The first reports of cardiotoxicity with ifosfamide were supraventricular arrhythmias and ST-T wave changes. Later studies showed an acute (mean 12 days) and dose-dependent cardiomyopathy in 17 % of patients treated with high-dose ifosfamide; at doses of 12.5 mg/m^2, only one of 12 (8 %) of patients developed congestive heart failure; however, at doses of 16 g/m^2 and 18 g/m^2, four of 12 (33 %) and two of three (67 %), respectively, developed congestive heart failure [30, 31].

Protein kinase inhibitors

Protein kinase inhibitors are a group of anti-neoplastic agents that predominantly target tyrosine kinases and have revolutionized the treatment of several cancers such as chronic myelogenous leukemia (CML), renal cell carcinoma, hepatocellular carcinoma, and melanoma [32].

Protein kinase inhibitors, particularly those targeting the VEGF receptor, can cause cardiomyopathy [32–36]. Sunitinib, approved for the treatment of gastrointestinal stromal tumors, renal cell carcinoma, and pancreatic neuroendocrine tumors, is associated with up to 28 % risk of

reduction in LVEF by ≥10 and 15 % risk of symptomatic HF [33, 34, 36]. In a meta-analysis of 6935 patients treated with sunitinib, the incidence of HF was 4.1 % with a relative risk of 1.81 compared to placebo [37]. In the clinical trial that led to approval of sunitinib for metastatic renal cell carcinoma, the cardiomyopathy seen in 21 % of patients was completely reversible; however, in a report of six patients treated at M.D. Anderson, sunitinib-induced heart failure was not completely reversible [35, 36]. The risk of cardiomyopathy or symptomatic heart failure with sorafenib is not well established, but in an observational study 33.8 % of patients treated with sunitinib or sorafenib experienced a cardiac event [38]. Biopsy of human and mouse cardiac myocytes revealed myocyte apoptosis [32, 34].

Lapatinib is a small molecule dual tyrosine kinase inhibitor targeting EGFR (ERBB1) and HER-2 kinases, used in the treatment of advanced or metastatic HER-2-positive breast cancer. In a pooled analysis of 44 phase I studies, a cardiac event (symptomatic HF or ≥20 % decline in LVEF) was seen in 60 of 3689 patient (1.6 % of patients) and 0.2 % experienced symptomatic HF. Of these patients, 35 of the 40 who had a determined outcome recovered LVEF [39].

Imatinib is a small molecule inhibitor of the Bcr-Abl tyrosine kinase of Philadelphia chromosome-positive CML. Heart failure is a rare, but recognized, adverse effect of treatment with imatinib which appears to be associated with increasing age and preexisting cardiac risk factors [40–42].

See Table 1 for a summary of agents associated with chemotherapy-induced cardiomyopathies.

Diagnosis

The definition of chemotherapy-induced cardiomyopathy is not well established. It is reasonable to use the definition of the independent cardiac review and evaluation committee for trastuzumab trials which requires at least one of the following: (1) decrease in LVEF either global or more severe in the septum; (2) symptomatic CHF; (3) S3 gallop, tachycardia, or both; and (4) decline in LVEF of ≥5–<55 % with signs or symptoms of CHF, or a decline in LVEF of ≥10–<55 % without accompanying signs or symptoms [13]. The American Society of Echocardiography and European Association of Cardiovascular imaging defines cancer therapeutics-related cardiac dysfunction as a decline in LVEF of >10 % to a value <53 % [43]. This statement further categorizes the decline in LVEF as symptomatic versus asymptomatic and reversible versus irreversible versus indeterminate [43]. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 uses a grading system to define heart failure: 1—asymptomatic with laboratory or cardiac imaging abnormalities; 2—symptoms with mild-to-moderate activity or exertion; 3—severe with symptoms at rest or with minimal activity; 4—life-threatening consequences requiring urgent intervention, 5—death.

The diagnosis of chemotherapy-induced cardiomyopathy involves a multi-disciplinary approach between oncology and cardiology and starts with a detailed history of risk factors and exposures followed by physical exam and basic cardiac evaluation (ECG and LVEF evaluation). Endomyocardial biopsy is both sensitive and specific for anthracycline-induced cardiotoxicity; however, sampling variability and invasive nature limit clinical utility [44–46]. In cases of unclear diagnosis, endomyocardial biopsy remains the gold standard.

The role of cardiac biomarkers in early detection and prediction of patients who will develop LVSD is undefined, but early studies have shown promising results. Cardiac troponin I, high-sensitivity cardiac troponin T, and brain natriuretic peptide (BNP) can predict development of cardiomyopathy [47–53]. In the largest study, 703 patients undergoing various high-dose chemotherapy regimens, the patients at greatest risk of cardiac events were those who had both early and late (1-month post-chemotherapy) elevations in troponin I [53]. Cardiac biomarkers have the benefit of detecting myocardial damage before functional impairment evolves and, compared to some of the imaging modalities described below, are inexpensive and widely available.

Noninvasive imaging remains the cornerstone of monitoring and diagnosis. Radionuclide ventriculography (RVG) was the modality employed to quantify LVEF in most early studies on the cardiotoxicity of antineoplastic chemotherapy and provides accurate and highly reproducible measurement of LVEF. RVG accurately predicts the risk of HF and, when used as part of guideline driven treatment protocol, can prevent development HF in patients treated with doxorubicin [54, 55].

Echocardiography is the most widely used method for tracking changes in LVEF over time because it is easily obtained and does not expose patients to radiation or contrast. It also provides information about valve function, pulmonary pressures, and pericardial pathology. Decreased reproducibility relative to RVG, due to geometric assumptions required to calculate EF and interobserver variability, is a limitation. An optimal study is often difficult to obtain due to patient specific limitations such as obesity, shadowing, and left-sided breast implants. Recent studies have shown that advanced echocardiography modalities, tissue velocity and strain imaging, are able to detect small changes in patients treated with cardiotoxic chemotherapy who will go on to develop cardiomyopathy

Table 1 Chemotherapeutic agents associated with cardiomyopathy

Agent	Mechanism	Incidence	Time course	Prognosis
Anthracyclines				
Doxorubicin	Free radical damage Induced apoptosis DNA damage Alteration in ATP	5 % at cumulative dose 400 mg/m^2 26 % at 550 mg/m^2 48 % at 700 mg/m^2	Acute Early-onset chronic progressive (<1 yr)	Typically not reversible
Epirubicin		0.9–3.3 %	Late-onset chronic progressive (>1 yr)	
Idarubicin		5–18 %		
Liposomal doxorubicin		2 %		
Monoclonal antibodies				
Trastuzumab	Antibody-mediated cardiac myocyte damage via ErbB2 inhibition in cardiomyocytes	3–8 % given alone Up to 27 % when given concurrently with doxorubicin	Not well defined, but typically within months	Reversible, mean recovery 1.5 months, most within 6 months
Bevacizumab	Antibody-mediated cardiac myocyte damage via VEGF Inhibition	1.6 %	*	*
Alkylating agents				
Cyclophosphamide	Hemorrhagic myocardial necrosis possibly due to free radical damage	7–28 % dose related	Acute (days to weeks)	Variable, median recover 78 days
Ifosfamide		17 % in high-dose ifosfamide	Acute (mean 12 days)	Variable
Protein kinase inhibitors				
Sunitinib	Induction of myocardial apoptosis via multifactorial effects of tyrosine kinase inhibition	4.1–28 %	Mean onset 22 days	Reversible
Sorafenib		*	*	Reversible
Lapatinib		0.2 %	Mean onset 13 weeks	Reversible, mean recovery 7.3 weeks
Imatinib	Induced myocyte death via mitochondrial damage	Rare, 1.7 % in pooled analysis	*	*

* Insufficient data

[50, 56, 57]. Further, 3-D real-time TTE has been shown to correlate very well with MRI ($r = 0.91$) for assessment of LVEF at 12 months in a cohort of patients with breast cancer on chemotherapy [58].

Cardiac magnetic resonance imaging (CMR) is the gold standard for estimating cardiac volumes and LV function and does not expose patients to ionizing radiation. CMR is not well studied or validated in oncology patients compared to other modalities; however, it may be particularly useful when 2-D and 3-D echocardiographic measurements of LVEF fall below 50 %, and in patients for whom discontinuation of chemotherapy is being considered, in order to obtain the most accurate measurement [43]. CMR is also limited by availability and patient characteristics such as magnetic prostheses, chronic renal failure, arrhythmias, and claustrophobia. See Table 2 for a summary of the benefits and limitations of various modalities used in the detection and monitoring of chemotherapy-induced cardiomyopathy.

Prevention

Many agents have been studied for the prevention of anthracycline-induced cardiomyopathy. In a recent meta-analysis of 12 randomized control trials and two observational studies, the protective benefit of statins, dexrazoxane (DRZ), beta-blockers, and angiotensin antagonists was compared [59]. Although there was significant heterogeneity in the studies, all agents were shown to have a statistically significant protective effect on anthracyclines-induced cardiomyopathy [59].

Dexrazoxane

DRZ, a topoisomerase II beta inhibitor and iron chelator, is the best-studied agent for the prevention of anthracycline-induced cardiomyopathy. Studies show that DRZ is cardioprotective without reducing the desired effect of the chemotherapeutic agent [60–64]. According to the American

Table 2 Comparison of diagnostic modalities

Diagnostic modality	Benefits	Limitations
Troponin BNP	Potential for early detection before decline in LVEF	No measurement of LVEF
	Noninvasive	
Echocardiography	Easily obtained	Less accurate than other modalities
	No exposure to ionizing radiation or contrast	Limited by patient characteristics such as BMI
	Evaluation of valve structures, pericardial etc.	Tissue Doppler, 2-D strain and 3-D strain imaging overcome many of the limitations of traditional echocardiography
RVG	Accurate and highly reproducible measure of LVEF	Exposure to ionizing radiation
		Limited data beyond LVEF
	Most well studied in chemotherapy cardiomyopathy	
CMR	No exposure to ionizing radiation	Limited data in chemotherapy-induced cardiomyopathy
	May help to differentiate between other suspected etiologies for heart failure	Patient specific limitations (renal failure, arrhythmias, prostheses)
		Availability in nonacademic centers
Endomyocardial biopsy	Definitive tissue diagnosis	Invasive
		Does not provide interval data
		Subject to sampling error

Society of Clinical Oncology (ASCO), DRZ may be considered for patients with metastatic breast cancer and other malignancies who have received a cumulative dose of doxorubicin $\geq$300 mg/m^2 [65]. Delayed administration is recommended because the cardioprotective effect of DRZ is present whether started before or after 300 mg/m^2 cumulative dose is reached, and concern remains that DRZ may impact the anti-tumor effect of chemotherapy [61]. DRZ is not recommended for patients with metastatic breast cancer initiating treatment with doxorubicin or patients receiving adjuvant doxorubicin for breast cancer [65].

Beta-blockers

Carvedilol has been studied in both animal and human models for a cardioprotective effect. The first human study randomized patients treated with anthracyclines to carvedilol or placebo and found a significant cardioprotective effect on both LV systolic and diastolic function [66]. In the OVERCOME trial, a prospective randomized control trial of patients with hematologic malignancies, concurrent carvedilol, and enalapril resulted in an absolute difference of 3.1 % units in LVEF compared with placebo [67]. A larger retrospective observational study of patients treated with anthracyclines and trastuzumab who happen to be on beta-blockers found a similar protective effect on incidence of heart failure (hazard ratio 0.2) [68]. Although not designed to study statins, a similar protective effect of statin therapy was found (HR 0.3) [68]. More recently a randomized controlled trial of nebivolol, a beta-1 selective agent with vasodilatory effects mediated by NO release, in breast cancer patients treated with anthracyclines showed a statistically significant cardioprotective effect on LV end systolic diameter (LVESD), LV end diastolic diameter (LVEDD), and LVEF [69]. The mechanism of beta-blocker cardioprotection in anthracyclines may be related to antioxidant effects of carvedilol and nebivolol [66, 69].

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)

Enalapril is effective in preventing LVSD in a diverse group of high-risk cancer patients [70]. In a study by Cardinale et al. [70], patients with elevations of troponin I shortly after high-dose chemotherapy were randomized to enalapril or placebo. Forty-three percent of the control subjects and 0 % of patients in the ace inhibitor group showed a decrease in LVEF of $\geq$10 % and below normal lower limit of 50 % ($p < 0.001$) [70]. This study is of particular interest because enrollment was limited to only those patients receiving high-dose chemotherapy who were found to have an elevated troponin I level during or shortly after chemotherapy. Absence of troponin elevation during or shortly after chemotherapy had previously been demonstrated by the same investigators to have a very high negative predictive value for development of LV systolic dysfunction or adverse cardiac events [47]. As noted above, enalapril in conjunction with carvedilol has cardioprotective effects for preventing LVSD [67]. The PRADA trial is an ongoing placebo-controlled, double-blind trial to determine whether ARBs (candesartan), beta-blockers (metoprolol), or their combination are effective in

preventing LVSD in patients treated with adjuvant epirubicin with or without trastuzumab [71].

Statins

The cardioprotective benefits of statins are well known and studied. Statins decrease oxidative damage by stabilizing mitochondria and decreasing vascular inflammation [72, 73]. In a retrospective cohort study of 628 newly diagnosed breast cancer patients treated with anthracyclines, uninterrupted statin therapy had a cardioprotective effect against heart failure (HR 0.3) [74]. Of note, the primary outcome in this study was heart failure requiring hospital admission, as opposed LVSD. In a randomized control trial of 40 patients treated with doxorubicin, prophylactic atorvastatin was effective in maintaining LVEF compared to placebo [75].

Treatment

There are limited data regarding the treatment of chemotherapy-induced cardiomyopathy; however, patients with asymptomatic reduced LVEF and symptomatic HF should be treated according to standard heart failure guidelines [76]. ACE inhibitors have shown benefit when started for anthracycline-induced LVSD. In a study by Cardinale et al. [77], enalapril treatment resulted in complete recovery of LV systolic function in 64 % of patients if initiated within 2 months of chemotherapy. This effect diminished as time elapsed from chemotherapy treatment and approached zero at 12 months [77].

A 2010 study highlights the need for oncologists and cardiologists to improve treatment of patients with chemotherapy-induced cardiomyopathy [78]. In this study, only 31 % of patients with asymptomatic LVSD were treated with ace inhibitors or ARB and 35 % were treated with beta-blockers [78]. In contrast, for patients with symptomatic LVSD, 67 % were treated with an ace inhibitor or ARB and 100 % of patients were treated with a beta-blocker [78].

Conclusion

Heart failure and asymptomatic LVSD remain clinically important adverse effects of cytotoxic as well as of the newer, so-called targeted antineoplastic drugs. A multidisciplinary approach is required to provide patients with optimal prevention, monitoring, and treatment strategies.

Compliance with ethical standards

Conflict of interest Drs. Angela Y. Higgins, Thomas D. O'Halloran, and James D. Chang declare that they have no conflicts of interest or financial ties to disclose.

Statement of human rights This article does not contain any studies with human participants performed by any of the authors. The manuscript is a review of literature and does not contain novel clinical studies or patient data.

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