short review

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Cardiotoxicity—current recommendations of prevention and treatment

Jutta Bergler-Klein

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Summary Tremendous advances in modern oncology therapies enable an increasing life expectancy of many cancer entities. Short or long-term cardiovascular side effects, however, gain importance. The current review focuses on recent recommendations for strategies of preventing and treating cardiotoxicity. A personalized assessment of the baseline risk of cardiotoxicity is recommended in all patients, without delaying the initiation of the cancer therapy. A baseline ECG, biomarkers (NT-proBNP, troponin), blood pressure and echocardiography should be obtained in all patients scheduled for potentially cardiotoxic treatments. Cardiac risk factors, e.g., coronary disease, hypertension, elevated lipids, should be promptly treated and optimized. Increased surveillance with more frequent cardiac imaging and sequential biomarker assessment during the cycles is recommended in high-risk cardiac patients. New imaging methods in echocardiography such as speckle tracking global longitudinal strain reflecting early myocardial ventricular deterioration are proposed in recent recommendations. Signs of cardiotoxicity should induce early treatment by, e.g., ACE-inhibitors, beta-blockers and/or other heart failure therapies. Immune therapies, e.g., checkpoint-inhibitors can induce cardiac events such as arrhythmias, acute coronary syndrome with plaque rupture, or myocarditis, even in negative magnetic resonance imaging or normal echocardiography findings. Troponin, BNP and ECG may help to identify these potentially deleterious side effects. Furthermore, there is a bidirectional influence of heart disease and cancer, e.g., by common inflammatory pathways. Pre-existent heart disease leads to worse prognosis in cancer, necessitating close follow-up and cardiac treatment during cancer therapy. On the other hand, cardiovascular mortality is increased after cancer survival and periodic cardiac follow-up is recommended long-term especially after chemotherapy and-or radiation.

Keywords Cardio-oncology · Cardiac side effects chemotherapy · Cardiac surveillance in cancer therapy · Biomarkers · Echocardiography · Speckle tracking strain

Introduction

Significant advances in modern oncology therapies have led to increasing life expectancy of many cancer entities [1]. Therefore, short- and long-term cardiac side effects of oncology treatments progressively gain importance. Modern imaging methods and biomarkers can help to identify and predict cardiotoxicity in patients undergoing cancer therapies [2]. This review focuses on recent recommendations for strategies of preventing and treating cardiotoxicity.

Baseline individual risk assessment

In the recent position statement of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), a personalized approach evaluating the baseline risk of cardiotoxicity is recommended [3]. Patients scheduled to receive potentially cardiotoxic cancer therapies are stratified into three categories (low, medium, or high risk), depending on therapy- and patient-related factors [3]. Therapy-related factors include type and dose of anticancer agents, as well as previous cancer therapies (e.g., anthracyclines, radiation), whereas patient-related factors consist of

A.o. Univ. Prof. J. Bergler-Klein, MD, FESC, FEACVI, FHFA (✉)
Department of Cardiology, Medical University of Vienna, Waehringer Guertel 18–20, 1090 Vienna, Austria
jutta.bergler-klein@meduniwien.ac.at

age, pre-existent cardiovascular risk factors such as coronary disease, hypertension, heart failure, atrial fibrillation, valve disease, or other comorbidities such as diabetes [3]. Specific proformas may be applied to quantify the overall risk in a total point score [3].

A reduced or even low-normal/borderline left ventricular ejection fraction (LVEF) of 50–54% in echocardiography before start of cancer therapy categorizes the patient at increased risk of cardiotoxicity [2]. It is therefore essential to assess the myocardial function even before cancer treatment in order to define a starting point for eventual deterioration during and/or after chemotherapy [2, 4]. Similarly, baseline elevation of the serum biomarkers troponin and/or B-type natriuretic peptide (BNP or NT-proBNP) point to an increased cardiotoxicity risk and further cardiac assessment may be needed.

It is highly endorsed that the baseline cardiovascular examinations should *not* delay the start of the cancer treatment [5]. If a high cardiac risk is identified, this should prompt initiation or optimization of cardiac treatment of many modifiable cardiac risk factors such as hyperlipidemia, hypertension, heart failure or coronary disease. If appropriate, possibly less cardiotoxic oncology therapy regimes may be considered, e.g., liposomal anthracyclines, or the addition of dexrazoxane. A multidisciplinary approach of cardio-oncology is emphasized in order to maximize possible benefit of cancer treatment in the individual patient despite any concomitant risk [5].

Cardiovascular surveillance, echocardiography, and biomarkers

Higher surveillance with more frequent cardiac imaging and biomarker assessment of serum troponin and BNP during the cycles is recommended in high-risk patients. The recent joint position paper on the role of cardiovascular imaging in cardiotoxic cancer treatments of the joint HFA/ESC and EACVI (European Association of Cardiovascular Imaging) depicts guidance especially for the timelines of echocardiography [4]. Local resources and availability of imaging may vary however, and costs may also limit current application.

A summary of how often echocardiography including left ventricular ejection fraction (LVEF) and speckle tracking global longitudinal strain (GLS) should be performed during specific therapies is shown in Table 1.

Different definitions of cardiotoxicity have been proposed. Recently, the ESC and EACVI, as well as ASE (European and American Society of Echocardiography), have defined cancer therapeutics-related cardiac dysfunction (CTRCD) as a decline in LVEF by >10% points below the LVEF cut-off 50% (EACVI/ASE: 53%). However, a normal LVEF as measured by the echocardiography biplane Simpson method does not always exclude underlying myocardial dysfunction. An inter- and intraobserver variability of up to 10% of LVEF measurements has been reported which would confuse cardiotoxicity interpretation.

Early subclinical myocardial damage may be identified by the recently established method of speckle-tracking echocardiography (global longitudinal strain, GLS) which also relates to elevated BNP. A reduction of GLS by 15% from baseline has been defined as pointing to the risk of developing consecutive LVEF reduction with overt cardiotoxicity. An impairment of GLS should prompt initiation of preventive cardiac heart failure therapy such as angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), and/or beta-blockers.

Similarly, a rise in BNP or troponin should lead to intensified cardiac treatment (e.g., ACE inhibitors, beta-blockers) and more frequent imaging, as suggested in the recent position paper on biomarkers [6]. Troponin reflects myocardial cell necrosis, e.g., in anthracyclines, or may be elevated in arrhythmias such as tachycardia atrial fibrillation, or due to renal insufficiency. A steep rise during immune checkpoint

Table 1 Summary of guidance for echocardiography timelines [2]

	Baseline	During therapy		After completion	
			Comment		Comment
Trastuzumab (in early invasive disease)	Yes	Every 4 cycles	Every 2 cycles in high risk, every 3 cycles in medium risk	6 months after final cycle	3 and 12 months after final cycle in high risk
Trastuzumab in metastatic disease (long-term therapy)	Yes	Every 4 cycles	Every 6 months when stable	Not indicated unless symptomatic	–
			More frequent in medium to high risk: every 2–3 cycles		
Anthracyclines	Yes	After completing cumulative does of 240 mg/m^2 doxorubicin	Every 2 cycles in medium to high risk	6–12 months after final cycle (depending on risk)	Reassess after 5 years (earlier in high risk)
VEGF and Bcr-Abl TKIs	In high-risk patients	Every 4 months during the first year	Every 6–12 months, when long-term therapy is necessary	No clear recommendations	–
Proteasome inhibitors	Yes	Every 6 months	Look for signs of amyloidosis	No clear recommendations	–
Immune checkpoint inhibitors	Yes (depending on baseline risk)	Immediately when cardiac symptoms occur. Every 6–12 months in long-term in high risk	CME if myocarditis suspected	No clear recommendations	Consider in high risk

GLS global longitudinal strain, *LVEF* left ventricular ejection fraction, *VEGF* vascular endothelial growth factor

Table 2 Confounders influencing serum troponin increase during cancer therapy

Coronary syndrome, plaque rupture
Vasospasm
Tako-Tsubo syndrome
Myocardial necrosis in anthracycline therapy, trastuzumab, radiation
Renal failure
Pericarditis
Myocarditis
Anemia
Sepsis
Blood pressure: hypertensive crisis, hypotension
Arrhythmias, e.g., atrial fibrillation, tachycardia
Hypertrophic cardiomyopathy
Amyloidosis
Pulmonary thromboembolism
Direct metastatic myocardial infiltration

Table 3 Confounders influencing serum NT-pro-BNP and increase during cancer therapy

Volume changes, intravenous fluid load, e.g., of chemotherapy
Renal failure
Anemia
Sepsis
Age, weight, gender
Blood pressure, hypertension
Arrhythmias, e.g., atrial fibrillation, tachycardia
Pulmonary thromboembolism
Coronary ischemia
Stiff heart, diastolic dysfunction, e.g., due to radiation
Myocarditis
Hypertrophic cardiomyopathy
Amyloidosis
Carcinoid valve disease

inhibitor therapy may identify immune myocarditis. Troponin increase may also point to ischemia with underlying coronary disease, hypertension or vasospasm, e.g., in fluorouracil (5-FU), capecitabine, or tyrosine kinase inhibitors, or plaques rupture in acute coronary syndromes necessitating coronary angiography and percutaneous coronary intervention (PCI; Table 2). BNP may be influenced by left ventricular volume status and pressure increase (Table 3).

Not only heart failure—cardiotoxicity also presents as arrhythmias, atrial fibrillation, e.g., in ibrutinib, or ventricular tachycardias, QT prolongation, hypertension, coronary syndromes and vascular disorders [7].

Bidirectional influence of heart and cancer

Cross talk and common pathways between tumor and the heart may induce release of biomarkers even before cancer therapy is started [8]. Hypoxia has been shown to trigger cancer growth in a mice model of myocardial ischemia by secretion of circulating factors inducing intestinal tumors, and a higher cumulative incidence of cancer in patients with heart failure 30 days after myocardial infarction was observed [9, 10]. Cardiovascular disease may promote cancer occurrence and progression. Inflammatory pathways, clonal hematopoiesis, hypoxia, as well as circulating microRNAs have been implicated in both atherosclerosis and cancer development, entitled as "reverse cardio-oncology" [11]. These common pathways emphasize the importance of optimal cardiac and heart failure therapy in order to prevent tumor incidence and/or progression.

Case

A 64-year-old woman with bilateral hereditary breast cancer (HOBC; right breast: invasive lobular carcinoma with ductal carcinoma in situ [DCIS], estrogen receptor [ER] positive, progesterone receptor [PR] negative, HER2 negative, Ki-67 40%; left: invasive ductal carcinoma with DCIS, ER/PR positive, HER2 negative, Ki-67 10%) was referred for cardiology consultation after surgical ablation of both sides for cardiac risk evaluation for chemotherapy.

Pre-existent hypertrophic cardiomyopathy with mesoventricular obstruction and restrictive diastolic function was known, with a left ventricular outflow tract gradient of 45 mm Hg accompanied by moderate to severe eccentric mitral regurgitation due to dynamic systolic anterior mitral leaflet motion (SAM) caused by the turbulent flow (Fig. 1). A history of stable angina pectoris on exertion, chronic slightly elevated troponin and previous cardiac decompensation with leg edema was present, as well as frequent ventricular extrasystoles without syncope and paroxysmal atrial fibrillation. A previous coronary angiography had excluded severe coronary stenosis. The ECG was remarkable with T-wave inversions in the chest leads.

With intensified cardiac monitoring in addition to the usual oncology follow-up, with echocardiography and serum biomarkers troponin as well as NT-proBNP before each cycle, the patient was able to undergo 4 cycles of epirubicin ($4 \times 90\,mg/m^2$) and cyclophosphamide ($4 \times 600\,mg/m^2$), followed by paclitaxel adjuvant (2 weeks per $80\,mg/m^2$) and docetaxel ($4 \times 100\,mg/m^2$). After the 3rd cycle of anthracycline, the patient reported intermittent dyspnea; however, no significant change in left ventricular function or biomarkers was observed and peripheral edema was not present. Due to low blood pressure, the cardiac medication was reduced intermittently. Therefore, the 4th cycle could be completed. Radiation is currently ongoing.

The current case shows that even high-risk cardiac patients can undergo their life-saving oncology treatment with close observation and monitoring.

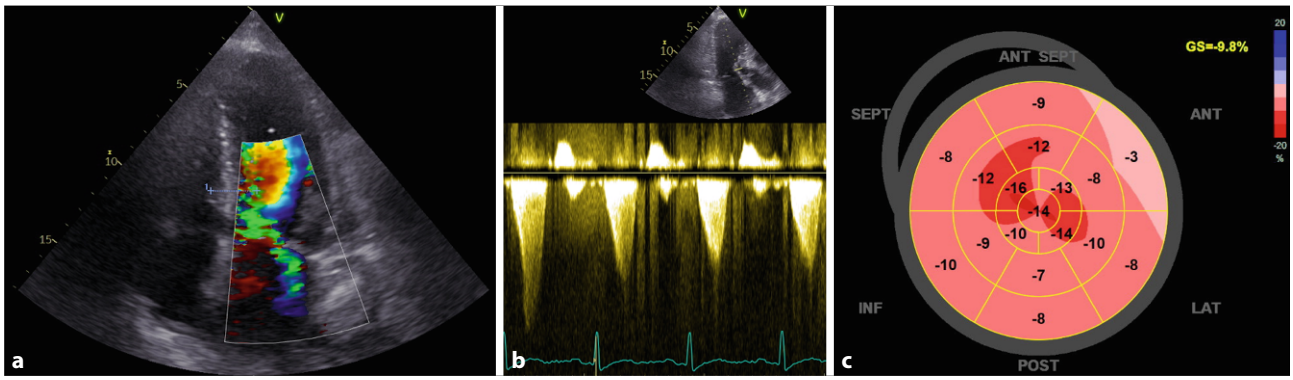

Fig. 1 Patient with hypertrophic obstructive cardiomyopathy undergoing chemotherapy for bilateral high-risk breast cancer (**a** echocardiography showing excentric mitral regurgitation with turbulent flow in the ventricular outflow tract; **b** continuous wave Doppler obstructive gradient; **c** example of global strain bulls-eye)

Conclusion

Early risk assessment and cardiac medication optimization without delaying the vital begin of oncology treatment can help to prevent cardiotoxicity development. While the frequency depends on the patient's baseline risk, assessment at least of the simple serum biomarkers NT-pro/BNP and troponin, as well as evaluation of left ventricular function and strain if available by echocardiography are helpful in predicting and detecting cardiac deterioration [12]. Increased cardiac therapy and oncology therapy adaptation if possible may enable continuation of treatment cycles [13]. More resources are needed for the establishment of dedicated cardio-oncology units.

Take home message

Baseline cardiac risk assessment in all and close follow up NT-proBNP, troponin, and echocardiography is recommended in high risk patients with cardiotoxic therapies. In survivors long-term cardiac follow up is necessary.

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Conflict of interest J. Bergler-Klein declares that she has no competing interests.

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