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REVIEW

Modern-day cardio-oncology: a report from the 'Heart Failure and World Congress on Acute Heart Failure 2018'

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Abstract

During the 'Heart Failure and World Congress on Acute Heart Failure 2018', many sessions and lectures focused on cardio-oncology. This important field of research is constantly growing, and therefore, a great amount of time during the congress focused on it. Prevention and early recognition of side effects is very important in cancer patients. One of the most common and potentially severe problems during antineoplastic therapy is cardiotoxicity. Hence, cardio-oncology is vital in managing cancer patients. This paper will summarize the topics discussed in three main sessions and many additional lectures throughout the 'Heart Failure and World Congress on Acute Heart Failure 2018'. The covered topics included pathophysiological mechanisms in the development of heart failure, risk factors, and early signs of cardiotoxicity detectable with different circulating and imaging biomarkers, as well as cardioprotective treatments recommended by different guidelines and position papers.

Keywords Heart failure; Cancer; Cardiotoxicity

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Introduction

Cardio-oncology has become a large, expanding, and important translational research area in modern medicine, which is gaining rapid interest.[1,2] Unfortunately, chemotherapy, immunotherapy, radiation therapy, and targeted therapies do not only effect cancer cells but also effect cardiomyocytes and vascular cells.[3] This can result into minor, asymptomatic cardiac lesions, detectable with circulating biomarkers or strain echocardiography, and also into life-threatening conditions, like severe heart failure (HF) or fulminant myocarditis.[4,5] During the 'Heart Failure and World Congress on Acute Heart Failure 2018', three full scientific sessions as well as a number of additional lectures within broader-subject sessions were dedicated to cardio-oncology. The sessions aimed to help improve the mechanistic understanding of cardiotoxicity as well as to help clinicians with practical advice and treatment strategies for cancer patients receiving potentially cardiotoxic oncology therapies. The congress was attended by 5881

participants with >300 faculty members from 47 countries and took place in Vienna, Austria, from May 26, 2018, to May 29, 2018.

The first cardio-oncology session started from pathophysiological studies on the crosstalk of HF and cancer mechanisms and then addressed how to approach cardiotoxicity in cancer patients with preclinical markers of left ventricular dysfunction (LVD) and in patients with confirmed cardiotoxicity. The second session discussed the prevalence of cardiac dysfunction in cancer patients and the underlying mechanisms. The third session reviewed the current recommendations and gaps in evidence from the different cardio-oncology guidelines and position statements. Additional lectures addressed cardiomyopathy in cancer and the prevention of HF. Detailed listing of all sessions can be found in *Table S1*.

Prevention and treatment of cardiotoxicity

In modern-day oncology, cardiotoxicity is a growing problem[1] and may be caused by cytotoxic chemotherapy, radiotherapy, molecular targeted therapies, and immune-modulating agents. In this scenario, active collaboration among different medical specialists is required to integrate cardiac imaging in cardio-oncology and to guide cardiovascular (CV) monitoring (*Figure 1*). Various definitions of CV toxicity exist depending upon the modalities used and whether clinical symptoms are required. Regarding direct myocardial toxicity, one common definition is a reduction of left ventricular ejection fraction (LVEF) by >10 percentage points and below the lower limit of normality (depending on local standard operating procedure 50–55%).[1] Cardiomyopathy in cancer is becoming an increasingly recognized entity, as Professor Dimitrios Farmakis from Athens, Greece, stressed during a session dedicated to cardiomyopathies. Besides anthracyclines, several additional agents may predispose to the development of cardiomyopathies, while recent evidence has shed some new light on the underlying pathophysiology. Professor Farmakis emphasized that the two main challenges of modern-day cardio-oncology are the integration of subtle cardiac dysfunction surrogates into clinical practice and proving that cardio-active therapies are effective in preventing cardiomyopathies in cancer patients.

Dr Teresa López-Fernández from Madrid, Spain, described the established relevant risk factors for developing cardiotoxicity: young (<18 years) or advanced age (>65 years), simultaneous chemotherapy with other potential cardiotoxic agents, previous radiation therapy, chronic kidney disease, and established CV disease or risk factors.[1,6] Consequently, before initiation of anti-cancer therapy treatment, it is important to assess the patient's individual risk of cardiotoxicity.[7] Dr López-Fernández highlighted the need to perform a baseline comprehensive CV screening, including echocardiography assessment, to exclude relevant cardiac problems and to optimize CV therapy when needed[8,9] (*Figure 2*). During and after cancer treatment, cardiac biomarkers and new echocardiography techniques are crucial in detecting LVD. Moreover, she recommended using an automated quantification of three-dimensional ejection fraction, as it requires less time and has a higher reproducibility.[10] Another important question is if cardiac monitoring just based on LVEF is enough. Serum cardiac biomarkers and deformation parameters have demonstrated to be more sensitive to detect subclinical myocardial damage.[1,11] An increase in cardiac troponins or a relative reduction of global longitudinal strain measured using speckle echocardiography by >15% from baseline can help identifying patients at increased risk of LVD with a good negative predictive value.[1,12] In addition, if LVEF remains within the normal limits, but subclinical damage is detected, Dr López-Fernández explained that these patients may benefit from additional cardioprotective medication [angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers, and/or beta-blockers] in order to reduce the risk of future events.[13] There is an urgent need for randomized, double-blind controlled trials to confirm such benefits because early HF treatment does

Figure 1 How to best deliver care.

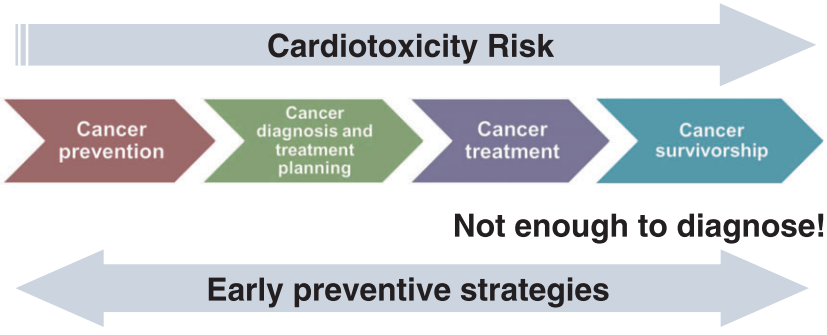

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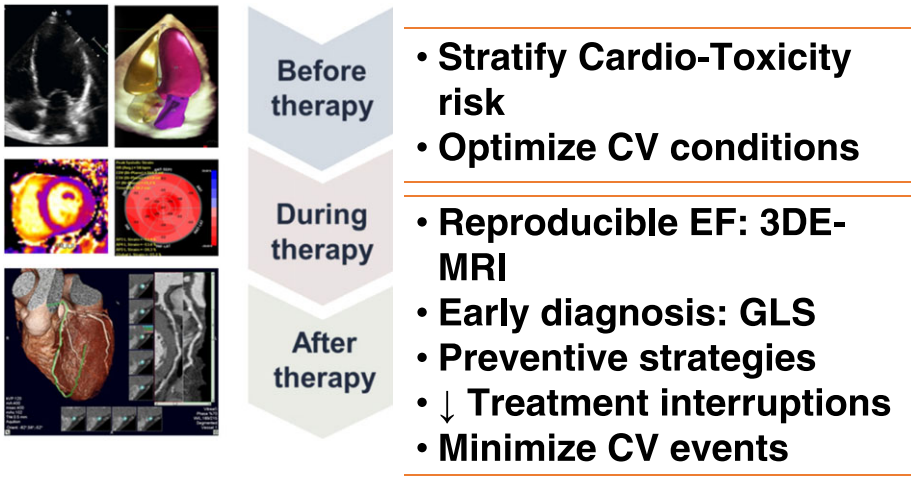
Figure 2 Role of cardiac imaging in cardio-oncology.



not always allow full recovery of ventricular function in patients who have developed cardiotoxicity. Recent data from Cardinale *et al*.[14] confirmed the need for early cardiotoxicity diagnosis. In 2625 patients treated with anthracyclines, with a prevalence of cardiotoxicity of 9%, it was demonstrated that 98% of events occur within the first year of treatment. If cardiotoxicity occurred, beta-blocker and ACE-inhibitor treatment were started and increased to the highest tolerated dose. With this therapy, a partial recovery of LVEF >50% was observed in 82% of patients, but only 11% of patients achieved a full LVEF recovery. If chronic HF develops nonetheless, it is associated with high treatment costs[15] and even on its own with disappointing 1 and 5 year survival rates of just 85 and 50%.[16–19] A very important part of modern-day research is the many different multi-centre registries.[20–23] They help us to better understand the diverse problems[24–26] and needs[27–29] of our patients in day-to-day life,[30–32] monitor the quality of treatment,[33–35] and identify new risk factors.[36,37]

Thus, the prevention of HF in cancer patients is very important. Professor Alain Cohen-Solal from Paris, France, addressed a study conducted in 273 low CV risk adult cancer patients treated with low cumulative doses of anthracycline chemotherapy called 'The International CardioOncology Society-One' trial.[38] There were two arms in the study: in the first, enalapril was only administered during chemotherapy cycles if troponin levels increased, and in the second, enalapril was administered before and during the entire chemotherapy regime. With regard to the occurrence of cardiotoxicity, both strategies resulted in similar results. The authors concluded that the administration of enalapril may be suitable for patients with an increase of troponin values during anthracycline treatment, and Alain Cohen-Solal emphasized that quick initiation of CV treatment after detection of subclinical LVD is vital in cancer patients.[39] During a session on prevention of HF, Professor Dimitrios Farmakis addressed the interaction between HF and cancer, two entities that share several common risk factors, while the one seems to increase the risk and worsen the outcome of the other. Professor Farmakis grouped the strategies for the prevention of HF in cancer into three main categories, including 'primordial prevention' that is applicable before cancer therapy in patients without any evidence of CV abnormalities, 'primary prevention' during cancer therapy in the presence of subtle abnormalities such as increase in cardiac biomarkers or worsening of left ventricular global longitudinal strain, and 'secondary prevention' during or after cancer therapy in the presence of clear LVEF decline. All three approaches are important in preventing HF in cancer patients.[40]

In the next congress presentation, Professor Thomas Suter from Bern, Switzerland, discussed the alternative clinical strategies to prevent cardiotoxicity. Professor Suter explained that in some cases, also non-anthracycline chemotherapies are an option, because these drugs are often associated with a lower chance of cardiotoxicity during treatment for high-risk patients but still can be effective in treating cancer.[1,41] Furthermore, to reduce the likelihood of LVD and cardiotoxicity even further in some patients, he reviewed using liposomal doxorubicin or concomitant dexrazoxane (DEX).[1,42] Newer options for cancer patients include targeted therapies like trastuzumab, which can also be associated with increased occurrence of cardiotoxicity.[43] Treatment duration of trastuzumab therapy is relevant to risk, and the benefit on HER2+ malignancies is significant and must be remembered when considering the risk:benefit balance.[44]

The intersection between cardiology and oncology

In patients with HF, many different co-morbidities can influence the patients' burden of disease.[45,46] Common

co-morbidities in patients with HF include iron deficiency,[47,48] anaemia,[49,50] liver dysfunction,[51,52] chronic kidney disease,[53,54] central sleep apnoea,[55,56] chronic obstructive pulmonary disease,[57,58] sexual dysfunction,[59,60] cachexia,[61,62] sarcopenia,[63,64] anorexia,[65,66] and also cancer.[67,68] Professor Rudolf De Boer from Groningen, the Netherlands, presented several studies, which have shown that cancer patients have an increased risk to develop HF and that patients with both, cancer and HF, demonstrate even worse prognosis than both diseases alone.[69,70] Interestingly, many cancers and HF share similar risk factors like hypertension, smoking, diabetes, and overweight.[71–73] Rudolf De Boer concluded that HF *per se* might promote tumour growth through inflammatory mechanisms and circulating biochemical factors.[74]

The relatively frequent occurrence of HF in cancer patients, which can lead to higher CV mortality[75] and worse overall prognosis, which is substantially attributed to anti-cancer therapy,[76] was discussed by Jochen Springer from Göttingen, Germany. New theories are being investigated, and it has been shown that cancer cells secrete factors (e.g. Ataxin-10) that interfere with the metabolism of cardiomyocytes and can cause wasting of the cardiac muscle,[77] which may result into a negative effect on prognosis.[67] Furthermore, cardiac muscle wasting in patients with lung, pancreatic, and gastrointestinal cancers has been shown recently.[78,79] Elevated circulating CV biomarkers, as predictors of mortality,[80] as well as impairments in the cardiopulmonary function,[81] were also found in chemotherapy naïve tumour patients. A recent multivariate survival analysis in patients with colorectal, pancreatic, and non-small lung cancer has shown that a resting heart rate $\geq$75 beats per minute was independently associated with worse survival.[82] This might represent an activation of the sympathetic nervous system like it has already been observed in patients with HF.[83] Consequently, more research into this area is needed to better understand systemic effects of cancer on the CV system.

Drs Javid Moslehi from Nashville, USA, and Carlo Gabriele Tocchetti from Naples, Italy, compared classical and new anti-cancer therapies and put an emphasis on different mechanisms of cardiotoxicity.[84,85] Substantial research is currently focused on understanding novel mechanisms of short-term and long-term effects of anthracycline cardiotoxicity on the heart muscle,[86] and also newer therapies like immunotherapies[87] and target therapies (e.g. tyrosine kinase inhibitors and trastuzumab)[88] have been shown to be associated with cardiac dysfunction in some patients.[1] Recently, immune checkpoint inhibitors have been shown to cause fulminant myocarditis.[89] Martin Štěrba from Hradec Králové, Czech Republic, discussed the potential use of ACE-inhibitors/angiotensin receptor blocker in prevention against chronic anthracyclines cardiotoxicity referring to rabbit models[90] and positive outcomes in the OVERCOME[91] and PRADA[92] trials. He also introduced the demanding necessity to better analyse the antioxidant mechanisms of DEX: in fact, a recent preclinical study[93] hypothesized that the depletion of topoisomerase 2β isoform, induced by DEX, might be the key process involved in the DEX cardioprotection.[94]

Breast cancer in a patient with heart failure

The management of HF in patients with breast cancer as a co-morbidity was discussed in this session, with regard to directives of the current guidelines. Dr Thomas Suter reported two different approaches towards HF with reduced ejection fraction and HF with preserved ejection fraction. In the first case, he said, it is recommended to avoid both anthracyclines and trastuzumab if LVEF is $<$40%. In general, chemotherapy drugs like taxanes and liposomal doxorubicin may be used to minimize cardiotoxic side effects.[95] When the patient is affected by HF with preserved ejection fraction, both anthracycline-based chemotherapy and targeted therapies can sometimes still be used, but it is important to discuss this in a multidisciplinary team and define appropriate screening intervals for clinical monitoring of the patients.

Guidelines on anti-cancer treatment in patients with HF were reviewed and analysed by Dr Alexander Lyon, London, UK, and gaps in evidence commented by Dr Markus Anker from Berlin, Germany. According to the current European Society of Cardiology 2016 position paper on cardiotoxicity,[1] patients with higher risk (lifestyle risk factors, CV risk factors, current cardiac disease, and previous cardiotoxic treatment) should be identified and surveilled, for example, by regular clinical echocardiographic examination and cardiac biomarker screening. In 2012, the 'European Society of Medical Oncology Cardiotoxicity Guidelines'[96] recommended frequent cardiac monitoring of patients with high-dose doxorubicin chemotherapy or/and pre-existing CV disease. In the 'American Society of Clinical Oncology Guidelines 2017',[97] the potential cardioprotective effect of DEX in high-risk patients was positively documented, but its administration to cancer patients is associated with more frequent occurrence of leukopenia with respect to a meta-analysis.[98] Moreover, Cardinale *et al.*[14] demonstrated that prompt cardioprotective intervention with combination of ACE-inhibitors and beta-blockers is a possible option for recovery of LVEF after early detection of cardiac damage in echocardiograms. The recent position paper from the Heart Failure Association Cardio-oncology Study Group provides a contemporary review and framework for the patient with HF who develops cancer.[74] Markus Anker also discussed the neutral double-blind, placebo-controlled CECCY[99] trial that assessed the use of carvedilol for the prevention of anthracycline toxicity in a low CV risk cancer population and noted a short period of follow-up time in this trial. He concluded that future

trials in cardio-oncology should have longer follow-up times, assess patients, who have a greater risk of cardiotoxicity, and test relevant (higher) doses of cardiotoxic chemotherapy.

Conclusions

During the 'Heart Failure and World Congress on Acute Heart Failure 2018', three sessions focused on the quickly growing field of cardio-oncology, along with some additional lectures during broader-themed sessions. The main focus of the sessions was how to recognize and treat cardiotoxicity in the clinical setting. More research including randomized clinical studies is needed to learn more about the prevention of cardiotoxicity and the long-term treatment of cancer patients with cardiac dysfunction.

Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Cardio-oncology sessions during 'Heart Failure and World Congress on Acute Heart Failure 2018'.

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