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Recent advances in cardio-oncology: a report from the 'Heart Failure Association 2019 and World Congress on Acute Heart Failure 2019'

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Abstract

While anti-cancer therapies, including chemotherapy, immunotherapy, radiotherapy, and targeted therapy, are constantly advancing, cardiovascular toxicity has become a major challenge for cardiologists and oncologists. This has led to an increasing demand of cardio-oncology units in Europe and a growing interest of clinicians and researchers. The Heart Failure 2019 meeting of the Heart Failure Association of the European Society of Cardiology in Athens has therefore created a scientific programme that included four dedicated sessions on the topic along with several additional lectures. The major points that were discussed at the congress included the implementation and delivery of a cardio-oncology service, the collaboration among cardio-oncology experts, and the risk stratification, prevention, and early recognition of cardiotoxicity. Furthermore, sessions addressed the numerous different anti-cancer therapies associated with cardiotoxic effects and provided guidance on how to treat cancer patients who develop cardiovascular disease before, during, and after treatment.

Keywords Cardiotoxicity; Heart failure; Cancer

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Introduction

More than 32 million people worldwide suffer from cancer.[1] In the last years, advances in anti-cancer therapies have led to an improvement in life expectancy of different cancer types.[2] These patients often suffer from multiple different co-morbidities that may develop as consequences from anti-cancer therapies. Frequent problems include, but are not limited to, chronic kidney disease,[3,4] liver dysfunction,[5,6] gastrointestinal disease,[7,8] anaemia,[9,10] fatigue,[11,12] infections,[13,14] anorexia[15,16], muscle wasting,[17,18] pain,[19,20] and heart failure (HF).[21,22] Depending on the cancer diagnosis and the type of anti-cancer treatment, cardiotoxicity rates may vary from 0% to 48% of patients, with HF being a

predominant presentation.[23] HF is associated with a 5-year survival rate of nearly 50%[24–26] and is frequently accompanied by reduced quality of life.[27] HF is characterized by multiple symptoms such as reduced physical performance,[28] shortness of breath,[29] fluid retention,[30] general weakness [31], and prolonged hospital stays[32], which ultimately also result into substantial healthcare costs.[33]

Besides HF, other frequent cardiovascular (CV) problems associated with anti-cancer therapies include coronary artery disease,[34] atrial fibrillation,[35] arterial hypertension,[36] thromboembolic disease[37], valvular disease[38], pulmonary hypertension,[39] stroke,[40] and peripheral vascular disease.[41] Special populations at increased short-term and long-term risks for CV disease are paediatric.[42] and elderly patients[43] Depending on the cancer entity, up to 30% of cancer patients eventually die of CV disease.[44]

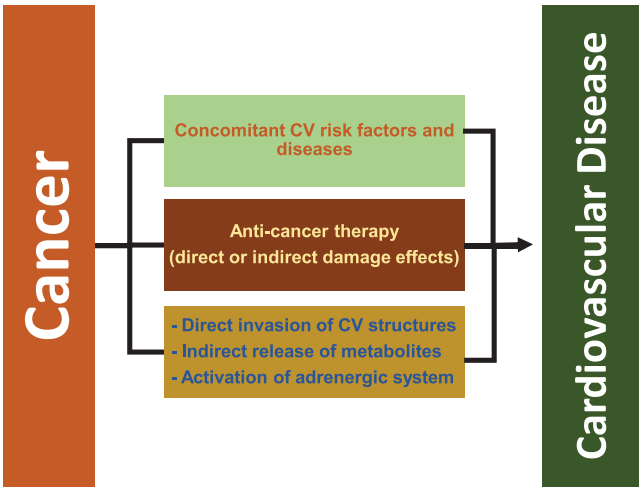
The 'Heart Failure and World Congress on Acute Heart Failure 2019' provided a great platform for experts in cardio-oncology to meet and exchange the latest ideas and advances in cardio-oncology. The congress was held in Athens, Greece, from 25 May 2019 to 28 May 2019, and was attended by 5431 delegates, including more than 285 faculty members in more than 120 scientific sessions. During the congress, four full-dedicated sessions, additional lectures, various clinical cases, and posters were dedicated to cardio-oncology. Experts in the field discussed how to identify, treat, and prevent CV problems in cancer patients and were involved in interactive discussions with the audience. A detailed list of all sessions can be found in Supporting Information, *Table S1*.

Cardiovascular disease in cancer

Cardiovascular events in cancer patients can be caused by three main factors: (i) concomitant CV risk factors and diseases; (ii) anti-cancer therapy (including chemotherapy, targeted therapy, immune checkpoint inhibitors, and radiation) through direct or indirect damage effects; (iii) cancer itself, through the direct invasion of CV structures or indirect release of metabolites and/or activation of adrenergic system[45–47] (*Figure 1*).

Dr Peter van der Meer (Groningen, the Netherlands), Dr Christian Bär (Hannover, Germany), and Associate Professor Dimitrios T. Farmakis (Athens, Greece) presented cancer therapy-related cardiomyopathy (CTRCM).[24,48] A recent 10-year follow-up study with 350 breast cancer survivors previously treated with chemotherapy and/or radiation therapy compared with 350 age-matched healthy women demonstrated an increased risk of mild left ventricular (LV) dysfunction in cancer survivors (15.3% vs. 7%).[49] These data underline a long-term risk for cardiac dysfunction in cancer patients previously treated with specific chemotherapy and/or radiotherapy.[23] The intersection between HF and cancer was explored by Associate Professor Farmakis and Professor Denise Hilfiker-Kleiner (Hannover, Germany). Both entities share several risk factors (ageing, tobacco, adiposity, physical inactivity, and infections) and an underlying systemic inflammatory status.[50–52] In the CANTOS trial,[53] which included 10 061 patients with myocardial infarction and increased high-sensitive C-reactive protein, the inhibition of the cytokine interleukin 1β with canakinumab (patients randomized to 50, 150, and 300 mg, or placebo) showed a reduction of nonfatal myocardial infarction, nonfatal stroke, or CV death with 150 mg canakinumab.[54] A secondary analysis of the data by Ridker *et al*.[55] showed a reduction of lung cancer incidence (with 150 and 300 mg canakinumab vs. placebo) and lung cancer mortality (with 300 mg of canakinumab vs. placebo). Further studies are needed to validate these results. Dr Markus Anker (Berlin, Germany) discussed CV problems of cancer patients beyond anti-cancer therapy

Figure 1 Aetiology of cardiovascular disease in cancer patients.

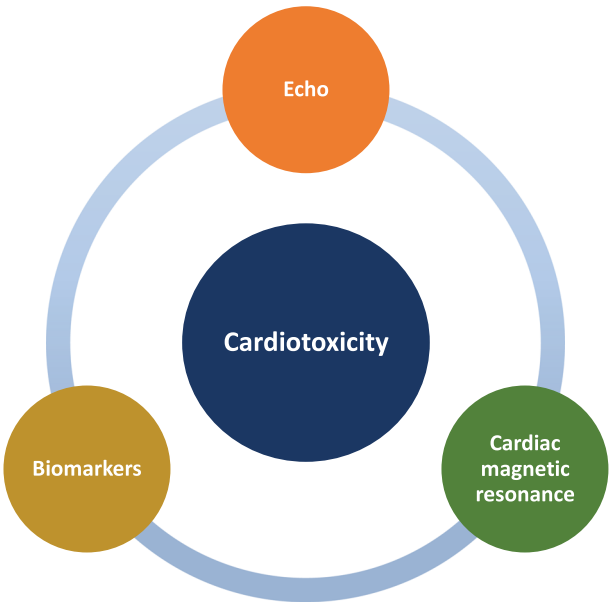


associated cardiotoxicity. It has previously been shown that treatment-naïve colorectal cancer patients also demonstrated a mildly reduced left ventricular ejection fraction (LVEF) compared with healthy controls of similar age and sex[56]. The resting heart rate of cancer patients has also been found to be an independent predictor of all-cause mortality in patients with pancreatic, colorectal, and non-small cell lung cancer[57]. This was confirmed in a large retrospective cohort of 4786 patients with breast cancer[58]. A recent analysis in 305 advanced colorectal adenoma patients suggested higher adenoma recurrence rates in those patients with higher heart rates[59]. These effects might be related to a sympathetic activation in some patients, like it has been shown for HF[60]. More studies are needed to better understand the underlying mechanisms.

Diagnosis and prevention

Dr Teresa Lopez-Fernandez (Madrid, Spain) addressed different cardiac imaging methods in cancer patients. Imaging is useful to stratify the risk profile at baseline, to predict recovery from cardiac injuries during cancer treatment and to detect early as well as late-onset of cardiac dysfunction in cancer survivors[61] (*Figure 2*). Dr Lopez-Fernandez accentuated the fundamental role of transthoracic echocardiography in modern day cardio-oncology, because it is ubiquitously available, involves no radiation exposure, and can also assess haemodynamics.[23] Cardiotoxicity, according to the 2016 ESC Position Paper on cancer treatments and CV toxicity,[23] is defined as a decrease of LVEF by >10 percentage points, below the local lower limit of normality (50–55%). According to recent opinions, 3D echocardiography may be preferable over 2D echocardiography (2DE) to assess LVEF in cancer patients, because of its low analysis time, higher reproducibility, and higher feasibility.[62,63] 3D echocardiography has demonstrated to outperform 2DE in detecting LVEF changes in cancer patients.[64] Global longitudinal strain has arisen as another parameter to characterize myocardial tissue in the past years. It permits the early identification of myocardial deformation abnormalities, with high reproducibility, before the detection of left ventricular systolic dysfunction (LVSD) by 2DE.[65] But much more research is needed into global longitudinal strain and its implications for the treatment of cancer patients.[66] In addition, Dr Lopez-Fernandez showed new data on right ventricle strain as a novel and sensitive predictor of cardiotoxicity.[67] Cardiac magnetic resonance is very accurate, has an excellent reproducibility, and allows tissue characterization of the heart.[23,68] However, Dr Lopez-Fernandez explained that cardiac magnetic resonance is not used in daily practice due to its high costs and limited availability only in larger clinical centres.

Figure 2 Diagnostic methods for early detection of cardiotoxicity.



Blood biomarkers as predictors of subclinical cardiotoxic injury were discussed by Dr Daniela Cardinale (Milan, Italy). Abnormal levels of troponins are considered a sensitive marker for cardiac monitoring to detect early cardiac-specific injury and asymptomatic LVSD in cancer patients during potentially cardiotoxic anti-cancer therapy,[69] and they are also used to stratify the risk of cardiotoxicity before cancer therapy.[70] Persistently increased N-terminal pro B-type natriuretic peptide during high-dose chemotherapy have also shown to predict long-term LVEF reduction in cancer patients.[71] Combined measurements of N-terminal pro B-type natriuretic peptide as markers of CV overload and troponins for myocardial injury during cancer therapy may be useful.[72] Lastly, microRNA were discussed as potential new biomarkers in cardio-oncology.[73]

Professor Radek Pudil (Hradec Kralove, Czech Republic) and Dr Kalliopi Keramida, (Athens, Greece) talked about different prevention strategies in order to minimize the development of CTRCM. The proposed approach consists of three different intervention phases according to the implementation of anti-cancer treatment. The aim of the first phase is to stratify the patients into low-risk, medium-risk, and high-risk groups for cardiotoxicity during anti-cancer treatment.[74] The identification of high-risk patients is important in order to apply adequate measures, including optimization of CV risk factors and pre-existing CV disease, planning of active screening during therapy and interdisciplinary cardio-oncologic decisions for the anti-cancer treatment with the best benefit/risk ratio.[75] Additionally, beneficial effects of exercise training before and during cancer therapy have been demonstrated.[76–78] The second phase concentrates on identifying patients with LVSD during treatment. Frequently used

and inexpensive screening tools include serial troponin measurements and regular echocardiographic monitoring of LVEF.[23,79] Both speakers agreed that in case of cardiac dysfunction, a decision for continuation of treatment of the patient can only be made by the close collaboration between cardiologists and oncologists.[23] The third phase of prevention consists of long-term surveillance of cancer survivors. Associate Professor Farmakis quoted a study by Mertens *et al*.[80] in 20 227 childhood cancer survivors that found cardiac mortality to be 8.2 times higher compared with the general population with no previous cancer diagnosis. CV disease can develop many years after diagnosis and treatment of cancer.[81] Associate Professor Farmakis recommended cardiologists to follow-up high-risk cancer patients after completion of anti-cancer treatment. Surveillance tools may include electrocardiograms, echocardiography, cardiac biomarkers, carotid ultrasound, fasting lipid profile, TSH in case of neck irradiation, and regular measurement of blood pressure.[23,82]

Cardio-oncology services have become very important and continue to grow in oncological clinical care. Dr Alexander Lyon (London, UK) and Dr Lopez-Fernandez discussed during their presentations how to establish such a service. Cardio-oncology services can help optimizing anti-cancer treatment, avoiding delays, and allowing adequate treatment of CV complications.[83] They also play a key role in the prevention of cardiotoxicity. Cardio-oncology units are composed of primary care departments, outpatient clinics, and educational programmes.[84] Recent data from Pareek *et al*.[84] demonstrated the effectiveness of these services. From 128 cancer patients with LVSD, 88% of patients were able to continue their cancer therapy after CV optimization, while an improvement of LVSD after 1 year of follow-up was shown in 94% of patients. Professor Thomas Thum (Hannover, Germany) recommended the promotion of basic, translational, and clinical research, training programmes, as well as educational resources as the foundation to a successful cardio-oncology workforce for the care of cancer patients. Lastly, the speakers also talked about the need to actively involve the patients in all decisions, so that patients can make informed decisions together with the treating physicians about possible treatment strategies.

Treatment of cardiotoxicity and new frontiers

Professor Alain Cohel-Solal (Paris, France) and Professor Rudolf de Boer (Groningen, the Netherlands) talked about available CV therapies to manage CTRCM. Because of its peculiar phenotype (tachycardia, low blood pressure, LV and/or right ventricular involvement, and dilated ventricles), intervention strategies may be challenging.[85] One of the largest studies regarding this question was conducted by Cardinale *et al*.[82] The authors followed 2625 cancer patients for a median of 5 years. During the first year of follow-up, echocardiography was conducted every 3 months, then for another 4 years every 6 months, and after that once a year. Cardiotoxicity was defined as a drop of LVEF below 50% and by >10 percentage points, which is similar to the current definition of cardiotoxicity by the ESC.[23] When cardiotoxicity occurred, HF therapy with angiotensin-conversion enzyme inhibitors (ACE-Is) and beta-blockers was initiated and up-titrated to the maximum tolerated dose. In the entire study, cardiotoxicity occurred in 221 patients (9%); 98% of all cardiotoxic events occurred within the first year of follow-up. This underlines the importance of closely monitoring cancer patients during the first year after a potentially cardiotoxic therapy. Of those patients with cardiotoxicity who initiated HF therapy with ACE-Is and beta-blockers, 82% had at least a partial recovery of LVEF. In patients, in whom ACE-I or BB therapy cannot be up-titrated due to adverse effects like hypotension, Professor Cohen-Solal considered ivabradine as a possible additional treatment for selected patients[86] and the need to be more cautious in drug titration in these patients than in other patients with cardiac dysfunction. There is also a need to investigate the effects and possible benefits of sacubitril/valsartan for the treatment of CTRCM.[87]

During the congress, the preliminary results of MADIT-CHIC Study (NCT02164721) by Singh *et al.*[88,89] were also discussed. Thirty patients (87% female) with CTRCM and lymphoma or breast cancer, which qualified for cardiac resynchronization–defibrillator therapy, participated in the trial. The primary endpoint, change of LVEF at 6 months, increased by 11% (95% CI 8–14; $P < 0.001$) and was independent of age, sex, NYHA class, and QRS duration. LV end-diastolic volume, LV end-systolic volume, and left atrial volume decreased. Weaknesses of the trial were the short period of follow-up, the primarily female patient population, the lack of control group, and only 30 included patients while the trial ran for 3.5 years. Larger randomized trials will have to further investigate the potential benefits of cardiac resynchronization–defibrillator therapy in CTRCM.

Dr Javid Moslehi (Nashville, TN, USA) focused on immune checkpoints inhibitors (ICIs). Immunotherapy (e.g. anti-CTLA-4, anti-PDL-1, and anti-PD-1) can be used as monotherapy or in combination with other chemotherapies, for example, in advanced melanoma[90] and advanced, refractory non-small-cell lung cancer.[91] Adverse events like myositis, mucositis, colitis, and pneumonitis can accompany the administration of these anti-cancer agents.[92] ICI-associated myocarditis is infrequently seen after the administration of 1-2 drug doses but associated with high rates of mortality of early 50%[93]. According to Dr Moslehi, a deeper understanding of the underlying pathophysiological mechanisms is urgently needed.[94,95] Therefore, specific knockout models in mice have been developed to further study ICI-related mechanisms and underlying

pathways[96]. Professor Carlo Gabriele Tocchetti (Naples, Italy) further deepened the concept about the importance of immunology in cardio-oncology:[97] not only can immunologic pathways be exploited to fight cancer[98] and predict the response to anti-cancer therapies[99] but also they are involved in the development of cardiotoxicity.[100]

Professor Dirk Brutsaert (Antwerp, Belgium) discussed how an impairment of the endothelium could influence the progress of HF and cancer. According to him, the endothelium has haemodynamic, mechanical, and biochemical sensors for several molecules like proteins, microvesicles, peptides, and microRNA.[101] As an organ with perfusion and transport function, endothelial cells secrete growth inhibitors and permit the extravasation of cells.[102] Professor Brutsaert therefore hypothesized that endothelial dysfunction might play an important role in the development of both cancer and HF.[103]

Conclusions

The 'Heart Failure and World Congress on Acute Heart Failure 2019' gave the participants a great overview of the current knowledge in cardio-oncology and new directions of this research area. Some of the cornerstones of cardio-oncology include the assessment of CV risk profiles in cancer patients before the initiation of anti-cancer treatment, the effective and adequate monitoring techniques for cardiotoxicity, the design of patient specific management strategies, and the need to universally introduce cardio-oncology services in hospitals working in close collaboration with oncology departments.

Conflict of interest

M.S.A. reports receiving personal fees from Servier. The UMCG, which employs R.A.dB. has received research grants and/or fees from AstraZeneca, Abbott, Bristol-Myers Squibb, Novartis, Novo Nordisk, and Roche. R.A.dB. received speaker fees from Abbott, AstraZeneca, Novartis, and Roche. D.F. has received speaker honoraria, consultancy fees, and/or travel grants from Abbott, Boehringer-Ingelheim, Daiichi-Sankyo, Menarini, Novartis, Pfizer, Roche, and Servier. S.vH. has been a paid consultant to BRAHMS/Thermo Fisher, Chugai, Helsinn, Boehringer Ingelheim, Grünenthal, Novartis, Roche, and Vifor. Z.I. reports lecture fees from Novartis, Pfizer, Boehringer Ingelheim, Bayer, Novo Nordisk, Astra Zeneca, and Eli Lilly. C.M. received personal fees from Servier, Boehringer Ingelheim, AstraZeneca, Bayer, Bristol-Myers Squibb, Novartis, Berlin Chemie, and Daiichi Sankyo. H.S. received speaker honoraria from Servier, Novartis, Boehringer, and Astra Zeneca. A.C.S. received personal fees (honoraria, grants, and travel expenses) from Novartis, Servier, Vifor, MSD, Astra Zeneca, Abbott, and Cytokinetics. C.G.T. was funded by a "Riceca di Ateneo/Federico II University" grant. A.J.S.C. has received fees from Astra Zeneca, Bayer, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Cardiac Dimensions, CVRx, Enopace, Faraday, Gore, Respicardia, Stealth Peptides, and V-Wave. A.R.L. has received speaker, advisory board or consultancy fees, and/or research grants from Pfizer, Novartis, Servier, Amgen, Takeda, Roche, Janssens-Cilag Ltd, Clinigen Group, Eli Lily, Eisai, Bristol Myers Squibb, Ferring Pharmaceuticals, and Boehringer Ingelheim. All other authors report no conflict of interest.

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 2019".

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