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An Overview of Cardio-Oncology, a New Frontier to Be Explored

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Advances in cancer treatments have led to an increasing number of cancer survivors, but also high rates of short- and long-term cardiovascular (CV) toxicities. The number of new cancer drugs is constantly increasing, and the uncertain CV toxicities of these drugs make long-term care and monitoring difficult. Moreover, traditional type I and type II cardiotoxicities may not be applicable to all of these agents. Multidisciplinary care with expertise in oncology, cardiology and other related specialties is required to mitigate cancer therapeutics-related cardiovascular dysfunction (CTRCD).

The aim of this review is to provide an overview of the main CTRCD, risk assessment, early diagnosis, and strategies for the prevention and management of patients receiving cancer therapies. There are still unmet needs for cardio-oncology researchers with regards to early detection measures, better treatment strategies, better follow-up protocols, and better management of CTRCD. Experts in cardiology, oncology, hematology, and radio-oncology should thus work closely in an attempt to foster patient awareness and research in this field, as well as call for support from public and industrial sources to initiate pivotal clinical trials to solve these unmet needs.

Key words: Cancer therapeutics-related cardiovascular dysfunction • Cardio-oncology • Cardiotoxicity • Chemotherapy • Radiotherapy

INTRODUCTION

The leading cause of death in Taiwan is cancer followed by cardiovascular disease (CVD),[1] and thus cardio-oncology (CO) is an emerging issue in Taiwan where cancer treatment has advanced rapidly over the past decades. The previous treatment triads, namely cytotoxic chemotherapy, radiation therapy and surgery, have been expanded to include targeted and immune-based therapies.[2] Thanks to the ever increasing number of advanced therapies available, an increasing number of cancer patients survive,[3] however an emerging issue associated with these new cancer therapies is sides effects on the cardiovascular (CV) system, which cause different spectrums of morbidity and mortality.[4] Cardiotoxicity refers to the direct harmful effects of cancer treatments on the CV system and/or the acceleration of CVDs in addition to traditional CV risk factors.[4,5] The origin of CO can be traced back to July 1st, 2000, when the MD Anderson Cancer Center initiated a comprehensive program to diagnose, treat and manage all CV disorders of cancer survivors. Currently, the main focus of CO research is on the prevention and management of related CV complications caused by cancer therapy, including: 1) treatment-based, including cancer-related medications, sur-

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gery, or radiation; 2) CV symptoms/complications; and 3) baseline CV risk-based identification and management. The goals of this article are to provide an overview of the major CV adverse events related to cancer chemo- and radiation therapies.

EVOLVING CONCEPTS OF CARDIOTOXICITY

Previous studies on cardiotoxicity have focused on anthracyclines and trastuzumab. Ewer and Lippman introduced the concept of type I irreversible, and type II reversible, cardiotoxicity.[6,7] Doxorubicin is the most well-known agent responsible for type I cancer therapeutics-related cardiovascular dysfunction (CTRCD). Since varying degrees of myocyte damage, including vacuolar swelling, myofibrillar disarray and cell death, can be observed in electron microscopy of myocardial biopsies, type I CTRCD is cumulative, dose-dependent and progressive. Therefore, there is a high probability of recurrent dysfunction with rechallenge, which may result in intractable heart failure or death without suitable interventions and adjustments in the chemotherapy regimen.[8] The characteristic agent of type II CTRCD is trastuzumab. Since this type of agent has not been observed to directly cause cell damage in electron microscopy of myocardial biopsies, the damage is not considered to be cumulative, dose-dependent or progressive. Therefore, it is relatively safe to rechallenge with a high likelihood of near recovery in 2-4 months after interruption (reversible).[8] Other anti-HER2-targeted therapies such as the monoclonal antibodies pertuzumab and trastuzumab emtansine, and the tyrosine kinase inhibitor lapatinib, appear to share this type II pattern of cardiotoxicity.[7,9] However, recent arguments against the concept of type I and type II cardiotoxicities have arisen, and doxorubicin-induced cardiotoxicity is not always irreversible,[10,11] while trastuzumab is not always reversible.[12] The type, timing, duration, and combination of drugs as well as the patient's genetic and comorbidity profile should all be taken into consideration when evaluating different patterns of cardiotoxicities. The speed of development of anti-cancer drugs continues to increase, and they have accounted for 27% of all new drugs in the United States since 2010, with approval of 126 cancer drugs to treat solid and hematologic tumors from 1980 through 2018 by the FDA (hyperlink: Cancer Drugs Account for Over a Quarter of All New Drug Approvals in the US - The ASCO Post). In view of this surge in new therapies, the practice of oncology and its related CTRCD are changing dramatically. Indeed, in addition to myocardial dysfunction (either cardiomyopathy, asymptomatic or symptomatic heart failure with preserved or reduced ejection fraction), CTRCD should include all kinds of toxic/side effects affecting the CV system, including hypertension, endothelial and vascular dysfunction, accelerated atherosclerosis, thrombosis and bleeding, pulmonary hypertension, pericardial disease, QT prolongation, conduction disease/arrhythmias, as well as radiation-induced CV disease.[5,13-18] In addition, different anti-cancer therapies (chemotherapy, targeted therapy, hormone therapy, immunotherapy, radiation therapy, and surgery) and bone marrow transplantation have their own relevant CV concerns. Table 1 summarizes the common CTRCD. Of note, only two types of CTRCD may not fit all clinical scenarios, and further studies are expected to clarify more types of CTRCD.

RADIOTHERAPY-RELATED CARDIOTOXICITY

Radiotherapy may cause damage to the pericardium, coronary arteries, valves, endocardium and myocardium, and symptoms can occur in the acute (< 6 months) or late phase (3-30 years).[19,20] Breast cancer patients with radiotherapy have been shown to have a 30% greater risk of coronary heart disease and a 38% greater risk of cardiac death compared to those without radiotherapy.[21] The CV risk has also been reported to be higher in patients receiving radiotherapy concomitantly with anthracyclines,[22,23] with a 1.4-fold higher risk of heart injury in patients with left-sided breast cancer than in those with right-sided breast cancer.[24] The direct CV risk of radiotherapy includes radiation volume and dose to which the heart and its substructures are irradiated,[25,26] and the rate of major adverse cardiac events (MACEs, i.e., myocardial infarction, coronary revascularization or CV death) has been shown to increase linearly by 7.4% per Gray increase in mean heart dose.[27] Risk mitigation is focused on reducing cardiac exposure to radiation, including displacement maneuvers such as prone positioning and deep inspiratory breath holding, custom blocks for

Table 1. Common cancer therapeutics-related cardiovascular dysfunction

Common anti-cancer therapy/common cardiovascular complications						
Anthracyclines (Doxorubicin, Idarubicin, Epirubicin)	v		v			
Alkylating agents (Cyclophosphamide, Ifosfamide)	v		v	v		
Antimetabolites (Clofarabine)	v		v			
Antimicrotubule agents (Docetaxel, Paclitaxel)	v		v	v		
Monoclonal antibodies (Trastuzumab, Bevacizumab, Pertuzumab)	v		v			
Protease inhibitors (Carfilzomib, Bortezomib)	v		v	v		
Fluoropyrimidines (5-FU, capecitabine, gemcitabine)	v		v	v		
TKIs (Sunitinib, Pazopanib, Sorafenib)	v	v	v	v		
VEGF inhibitors (bevacizumab)	v	v		v		
Arsenic trioxide, bortezomib, IL-2, methotrexate, mitoxantrone, rituximab, thalidomide, amsacrine, interferons			v			
Radiotherapy	v			v	v	v

 , left ventricular dysfunction /heart failure;  , hypertension and/or proteinuria;  , pericardium disease;  , arrhythmia/conduction problems;  , coronary artery disease/thrombosis;  , valve problems.

TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

the heart, intensity-modulated techniques, intraoperative irradiation and/or brachytherapy, and proton irradiation.[25,28,29]

IMMUNOTHERAPY-RELATED CARDIOTOXICITY

Immunotherapy-related cardiotoxicities have recently focused on chimeric antigen receptor T cell (CAR-T) therapy-associated cytokine release syndrome[30] and immune checkpoint inhibitor (ICI)-associated myocarditis. Although the reported incidence of ICI-related myocarditis is low (0.04-1.14%), it is associated with a high mortality rate (25-50%) and has been reported to occur early after the initiation of therapy.[13,31-34] While a review of 101 cases showed that 64% occurred after the first or second ICI dose,[33] another study found that some cases occurred after the first ICI dose.[32] In addition, combination ICI therapy has been reported to significantly increase the risk of myocarditis from 0.06% to 0.27%.[13,32] Other risk factors are ill defined, but may include underlying autoimmune diseases, diabetes mellitus and pre-existing CVD.[13,34-36] Although the diagnosis of myocarditis is challenging, elevated troponin and abnormal electrocardiography findings are common.[13,37] During myocardial edema, cardiac magnetic resonance (CMR), with late gadolinium enhancement, may be useful for an early diagnosis, however it is only present in < 50% of those with ICI-associated myocarditis.[37,38] An endomyocardial biopsy is the gold standard for diagnosis, but is often underused due to its invasive nature, risk of complications, and a lack of expertise in many hospitals.[37,39] The mechanism of myocarditis cardiotoxicity has been related to activated T cells,[40] and < 50% of patients have been reported to respond to high doses of corticosteroids or immunosuppressants.[13,41]

BASELINE RISK ASSESSMENT, EARLY DIAGNOSIS OF CTRCD AND STRATEGIES FOR THE PREVENTION AND TREATMENT OF CARDIOTOXICITIES

Some risk factors for cardiotoxicity in oncology patients are traditional risk factors for CVD such as smoking, age, obesity, and hyperlipidemia,[4,42,43] and some are newly identified genetic risk factors such as clonal hematopoiesis.[44] The modifiable risk factors will accelerate CTRCD if they are not well identified and/or well controlled. For patients with symptoms or signs of current cardiac dysfunction, the guidelines recommend further

assessing the risk using biomarkers such as troponins, natriuretic peptides, and the evaluation of left ventricular ejection fraction. Whenever possible, biomarker levels and imaging parameters should stay at baseline values throughout ongoing follow-up to ensure comparable information.[4] Echocardiography-based strain imaging may be particularly useful as the follow-up imaging tool.[45,46] A reduction in global longitudinal strain (GLS) of > 15% from baseline is generally considered to be abnormal and an early sign of left ventricular subclinical dysfunction[4] and an early indicator of heart failure. CMR with T1 and T2 mapping may be particularly useful to evaluate vascular and structural cardiotoxicities. Stress echocardiography, stress CMR, computed tomography angiography (CTA) and positron emission tomography are alternative options to evaluate ischemia in patients receiving therapies that may cause vasospasms or accelerate atherosclerosis.[46] The timing and frequency of follow-up will depend on various cancer treatments, cumulative anthracycline doses, delivery protocol and duration, as well as baseline CV risks.[4] Patients identified as being at high risk should be referred to a CO specialist.[4] The guidelines recommend measuring high-sensitivity cardiac troponins (cTnI or cTnT), B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) in those at high risk or undergoing cancer treatment.[4,47,48] The European Society for Medical Oncology (ESMO) guidelines in 2012 suggested that patients receiving adjuvant chemotherapy should receive serial monitoring of cardiac function at baseline, 3, 6 and 9 months during treatment, and then 12 and 18 months after the initiation of treatment, which is feasible and cost-effective in a National Health Insurance setting such as in Taiwan.[49] The ESMO guidelines recommend initiating cardioprotective agents [including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and/or beta-blockers] in patients receiving cardiotoxic treatment with decreased left ventricular (LV) ejection fraction, a decrease in GLS, or an elevation in cardiac troponin, with statins being considered in those with existing coronary artery disease.[47] The ASCO guidelines recommend dexrazoxane, although it is currently not available in Taiwan, to prevent cardiotoxicity in patients with high-dose anthracyclines (e.g. doxorubicin $\geq$ 250 mg/m^2).[45] Guidance from the European Society of Cardiology (ESC) suggests the use of cardioprotective drugs (ACE inhibitors, beta-blockers, ARBs) in patients with pre-existing clinical heart failure or significant LV dysfunction at baseline, and the initiation of cardio-protective agents in patients with elevated troponin during treatment with high-dose anthracycline regimens.[4]

CANCER-ASSOCIATED THROMBOSIS

Cancer-associated thrombosis (CAT) is a common complication and is also a major cause of mortality in patients with cancer. Patients with cancer are at a four- to seven-fold higher risk of initial venous thromboembolism (VTE), a three-fold higher risk of recurrent VTE, a two-fold higher risk of anticoagulation-associated bleeding, and a 10-fold higher risk of death from VTE compared to patients without.[50] In addition, patients with cancer have a two-fold higher risk of arterial thromboembolism than those without.[51] Risk factors for CAT can be classified into cancer-related (e.g., primary site, histology, grade, initial period after diagnosis, etc.), treatment-related [e.g., surgery/hospitalization, chemotherapy, antiangiogenics, central venous cannulation, erythropoietin stimulating agent/transfusion-related, etc.], patient-related (e.g., age, ethnicity, comorbidities, etc.) and some important biomarkers (e.g., platelet count, leukocyte count, hemoglobin, D-dimer, etc.).[52] Low-molecular-weight heparin (LMWH) has been shown to be more effective than warfarin for secondary prevention of VTE in cancer patients,[53] and previous guidelines recommend LMWH over warfarin in cancer VTE.[54] However, LMWH is inconvenient and painful for patients due to daily injections, and recent clinical trials (Hokusai-VTE Cancer, SELECT-D, CARAVAGGIO, and ADAM VTE) have proven that direct oral anticoagulants (DOACs) are noninferior to LMWH for CAT. Therefore, some DOACs (edoxaban, rivaroxaban, and apixaban) have become the mainstay in latest CAT treatment.[55,56]

UNMET NEEDS IN CARDIO-ONCOLOGY AND THE RECOMMENDED PROTOCOLS

The protocols for patient assessment and monitoring are based on expert consensus, and a nationwide trial or registry is still needed to determine which reco-

mmended protocol is most suitable. Currently there are no native clinical trials specifically designed to assess the prevention and management of adverse CV effects of cancer therapy, including the timing and choice of intervention. In addition, universal standardized definitions of cardiac endpoints in oncology trials are still lacking, and the awareness of CO for various health care professionals with regards to the long-term risks and need for follow-up still have to be advocated by societies of cardiology, hematology, oncology, and radio-oncology, and through electronic/public media to increase global patient awareness. The number of CO clinics in Taiwan is still limited, and more are needed to provide accessibility and adequate quality to more cancer patients receiving anti-cancer treatment. Only oncologists, radio-oncologists, cardiologists and other related specialties working together in multidisciplinary teams can increase the number of both cancer and CV survivors. Figure 1 summarizes our recommended protocols at baseline, subsequent follow-up, and suggested management when CTRCD events are suspected or encountered.

CARDIO-ONCOLOGY EDUCATION AND TRAINING

The JACC Cardio-Oncology Leadership Council recommends bidirectional CO fellowship training for Board-eligible or certified cardiologists/oncologists/hematologists to receive "Exposure and Basic Overview" level 1, "Advanced Clinical Experience and Knowledge" level 2, and "Cardio-oncology Fellowship" level 3 training to gain knowledge and experience of basic cancer biology, treatment principles and CV toxicities associated with solid and hematologic malignancy per se, team collaboration among rehabilitation, nurses, pharmacists, palliative care, in conjunction with the physical, psychological and social needs of the patients.[57] Information on new advances in cancer treatment and their CV complications should be periodically updated through cross-talk among cardiology/oncology/radio-oncology societies in order to formulate the best domestic protocols for CTRCD, and through data analyses from domestic trials/registry to contribute to practice guidelines.

AUTHOR CONTRIBUTIONS

The first author, Dr. Kai-Hung Cheng, participated in generating original ideas, in manuscript design and in drafting of the manuscript, in revising it critically for important intellectual content and in final approval of the manuscript submitted. Other authors participate in 1) conception and design and interpretation of collecting information: CMH, YWW and CJYH; 2) drafting of the manuscript or revising it for important intellectual con-

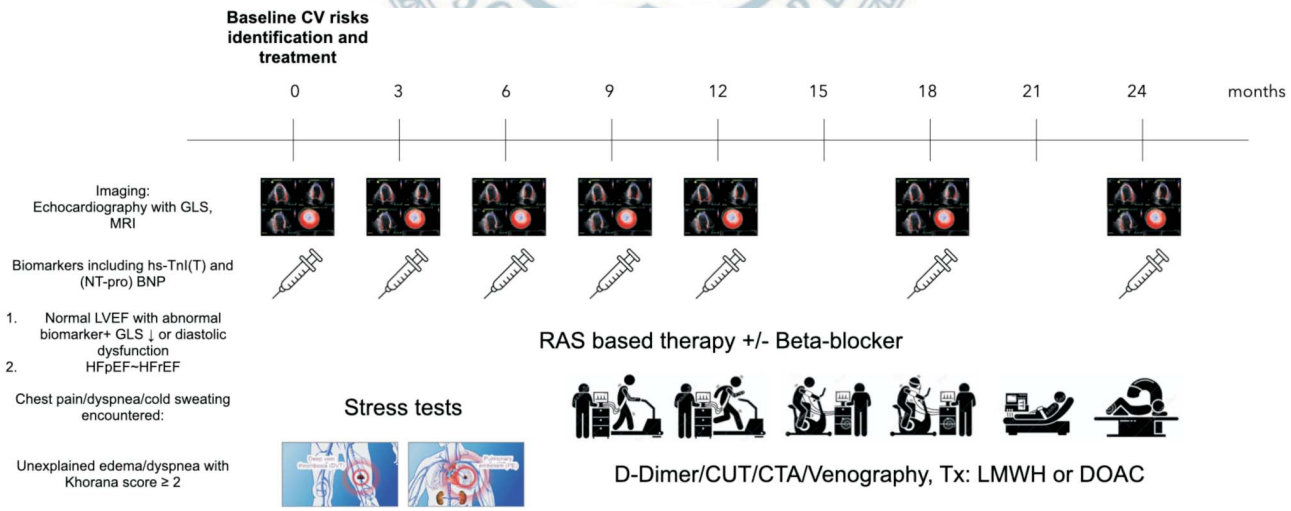

Figure 1. *Recommended protocol for baseline, follow-up and treatment. CTA, computed tomography angiography; CUT, compression ultrasound test; CV, cardiovascular; DOAC, direct oral anticoagulant; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-TnI (T): high sensitive troponin I or T; LMWH, low molecular weight heparin; MRI, magnetic resonance imaging; (NT-pro) BNP, B type natriuretic peptide or N terminal pro B type natriuretic peptide; RAS, renin-angiotensin system; Tx, treatment.*

tent: YWW and CJYH; and 3) All authors provided final approval for publication submission and revised the manuscript for important intellectual content.

DISCLOSURE SUMMARY

The authors have nothing to disclose.

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