

# Emergence, Development, and Future of Cardio-Oncology in China

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As the development of early detection and therapies advances in cancer patients, mortality rates attributed to cancer have declined. In the United States, there are approximately 15.5 million cancer survivors, and the number will grow to more than 20 million by 2026 (<http://www.cancer.org/cancer/news/news/report-number-of-cancer-survivors-continues-to-grow>). Unfortunately, the improved survival in cancer patients from cancer therapy is achieved at the expense of treatment-induced adverse effects with CVD being one of the most frequent side effects [Supplementary Table 1].<sup>[1]</sup> This may result from the direct cardiotoxicity of anticancer treatment or from the accelerated preexisting CVD or cardiovascular risk factors. CVD is now the second leading cause of long-term morbidity and mortality among cancer survivors.<sup>[2-7]</sup>

The presence of CVD may limit the treatment options for cancer. Here we share a case: A 60-year-old male patient with a 30-year history of smoking was diagnosed with non-ST-segment elevation myocardial infarction four years ago. Coronary angiography (CAG) showed 50% stenosis of the mid-left anterior descending (LAD) artery and 75% stenosis of the distal diagonal branch without percutaneous intervention. One year ago, he was diagnosed with squamous cell carcinoma of the left lung (cT<sub>3</sub>N<sub>2</sub>MX) and treated with afatinib. Due to the tumor progression, he underwent chemotherapy of gemcitabine and cisplatin in place of afatinib. On the 7<sup>th</sup> day of the second chemotherapy cycle, the patient presented with sudden and persistent chest pain with subsequent electrocardiogram demonstrating ST-segment elevation myocardial infarction. CAG confirmed the occlusion in the proximal LAD for which percutaneous coronary intervention treatment was provided. Gemcitabine was discontinued in the subsequent chemotherapy for the considering that the acute myocardial infarction may induced by gemcitabine. Such a case is one of the many that we have encountered where cancer was complicated by cardiovascular disease (CVD). Cardiovascular toxicity

induced by cancer treatment is a common and pressing issue for cardiologists and oncologists.

To sustain survival improvement achieved using modern cancer therapies, the importance of CVD in cancer patients has been increasingly recognized, leading to the emergence and development of the cross-disciplinary field of cardio-oncology. In 2000, the first onco-cardiology unit was established at the University of Texas MD Anderson Cancer Center, and in 2009, International Cardio-Oncology Society was established by the European Institute of Oncology.<sup>[8]</sup> The International Conference on Cancer and the Heart has been held in Texas every 2 years since 2010. Along with many publications from clinical and pathological observations or clinical trials, cardio-oncology specialists all over the world have been concentrating on their efforts in investigating epidemiologic burden, biomarkers and imaging for CVD prediction, and risk stratification and the effects of cardio-protective strategies. Just during 2016, four practice guidelines or consensus was published on the evaluation, prevention, and management of CVD in cancer survivors. These have set the foundation for this new discipline.<sup>[1,9-11]</sup> Recently, an opinion paper on cardiovascular toxicity related to anticancer treatment from the working group on cardio-oncology of the Korean Society of Echocardiography provided more information.<sup>[12]</sup>

As reported by the National Cancer Center of China, the incidence and mortality of cancer have increased

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significantly from 2000 to 2011 and there are now almost 10,000 new cancer diagnoses on average each day in China.<sup>[13]</sup> With the rapid development of cardio-oncology in Europe and US, it is increasingly being recognized among Chinese clinicians that it is critical to form a cross-disciplinary partnership in providing comprehensive CVD care for cancer survivors. In 2013, the Chinese Society of Clinical Oncology and the Chinese Medical Association published guidelines on the prevention and treatment of anthracycline-related cardiotoxicity and published updated version in 2017. In early 2016, a panel of 17 experts including cardiologists, oncologists, hematologists, cardiac imaging specialists, and basic research scientists initiated the China cardio-oncology network. The first workshop was held on June 5, 2016, in Dalian, China. Experts discussed the most appropriate approach to launch cardio-oncology in China. A second workshop swiftly followed on August 12, 2016, in Beijing, the group confirmed the concept and scope of the cardio-oncology program in China, which includes treatment-associated CVD in cancer patients, comorbidity of CVD and cancer, shared risk factors in cancer, and CVD and cardiac tumors.

Cardiovascular toxicity from chemotherapy, radiation therapy, targeted drug therapy, and surgery-related adverse effects<sup>[14-16]</sup> all contribute to the cardiovascular events in cancer patients. Age, preexisting CVD risk factors (smoking, obesity, sedentary habit, family history of premature CVD, etc.), specific chemotherapy agents and dosage, radiotherapy area, and dosage are common risk factors closely related to cardiovascular toxicity. According to the 2016 European Society of Cardiology (ESC) Position Paper on cancer treatments and cardiovascular toxicity, cardiovascular complications are classified into nine main categories: myocardial dysfunction and heart failure, coronary artery disease (CAD), valvular disease, arrhythmias, especially those induced by QT-prolonging drugs, arterial hypertension, thromboembolic disease, peripheral vascular disease and stroke, pulmonary hypertension, and pericardial complications.<sup>[1]</sup> An increasing body of evidence suggests that targeting modifiable risk factors, early prevention, and treatment can mitigate the degree of cardiotoxicity and early detection is increasingly important.<sup>[15-17]</sup> For example, prophylactic use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEIs/ARBs) or beta blockers could prevent anthracycline/trastuzumab-induced cardiotoxicity in adult cancer populations. The above-mentioned ESC Position Paper guideline provides screening and evaluation recommendations or suggestions for every category.

As illustrated in the case mentioned in the beginning of this article, acute myocardial infarction can be precipitated by targeted drug therapy and traditional chemotherapy in cancer patients with preexisting CAD. While cancer produces a hypercoagulable state, it also predisposes patients to bleeding, which limits options for medical and interventional therapies such as the use of antiplatelet drugs

and anticoagulants. Similarly, when a thromboembolic event or atrial fibrillation occurs in cancer patients, it is difficult to balance the bleeding risk and provide the more appropriate anticoagulation strategies. Although the current guidelines offer some general recommendations, clinical trials are urgently needed, especially on the suitability of these practice guidelines from Europe for Chinese cancer patients.

In recent years, as aging population becomes an increasing trend in China, a number of common risk factors presented in cancer and CVD patients, including obesity, diet, smoking, diabetes mellitus, and hyperlipidemia, become more prevalent.<sup>[18,19]</sup> As an example, there is convincing evidence supporting the correlation between obesity and esophageal adenocarcinoma, pancreatic, liver, colorectal, postmenopausal breast, endometrial, and kidney cancer. Epidemiological data suggest that up to 20% of malignancies could be related to weight gain and obesity.<sup>[20]</sup> As a report by the American Diabetes Association in 2010, there is convincing evidence associating colorectal, breast, endometrial, liver, pancreatic, and bladder cancers with diabetes mellitus.<sup>[21]</sup> In addition, treating CVDs and CVD-related risk factors may affect the risk and prognosis of cancer. For example, ACEI showed an association with breast cancer recurrence;<sup>[22]</sup> aspirin reduced the risk of colorectal cancer by 24%;<sup>[23]</sup> prediagnostic statin use reduces the risk of lethal prostate cancer;<sup>[24]</sup> and statin use either before or after diagnosis of cancer was associated with improved cancer specific as well as overall survival.<sup>[25]</sup> The overlap of risk factors in CVD and cancer suggests that the two seemingly different diseases might share some common biological molecular mechanisms such as inflammation, oxidative stress, and reactive oxygen species. Controlling CVD risk factors can help reduce the risk of cancer. Further understanding of the delicate interaction between CVD and cancer may lead to better prevention, earlier detection, and safer treatment strategies.

Cardiac tumors can be divided into primary and secondary cardiac tumors. A 20-year experience with review of 12,485 consecutive autopsies showed that their incidences are 0.056% and 1.23%, respectively. For secondary cardiac tumors, the common primary sources are carcinoma of the lung, breast, pancreatic, esophageal, liver, gastric and lymphoma, and leukemia.<sup>[26]</sup> Seventy-five percent of patients with cardiac tumors are benign.<sup>[27]</sup> Primary malignant cardiac tumors represented by sarcomas and non-Hodgkin lymphomas are rare and associated with a grave prognosis. Lestuzzi *et al.*<sup>[28]</sup> stressed the importance of the multidisciplinary approach and involvement of cardio-oncologists in making the diagnostic and treatment decisions. The prognosis may be improved by a careful planning of surgery and through the use of multimodality treatment including chemotherapy and radiation therapy. A strict follow-up protocol must be planned even following complete cure.

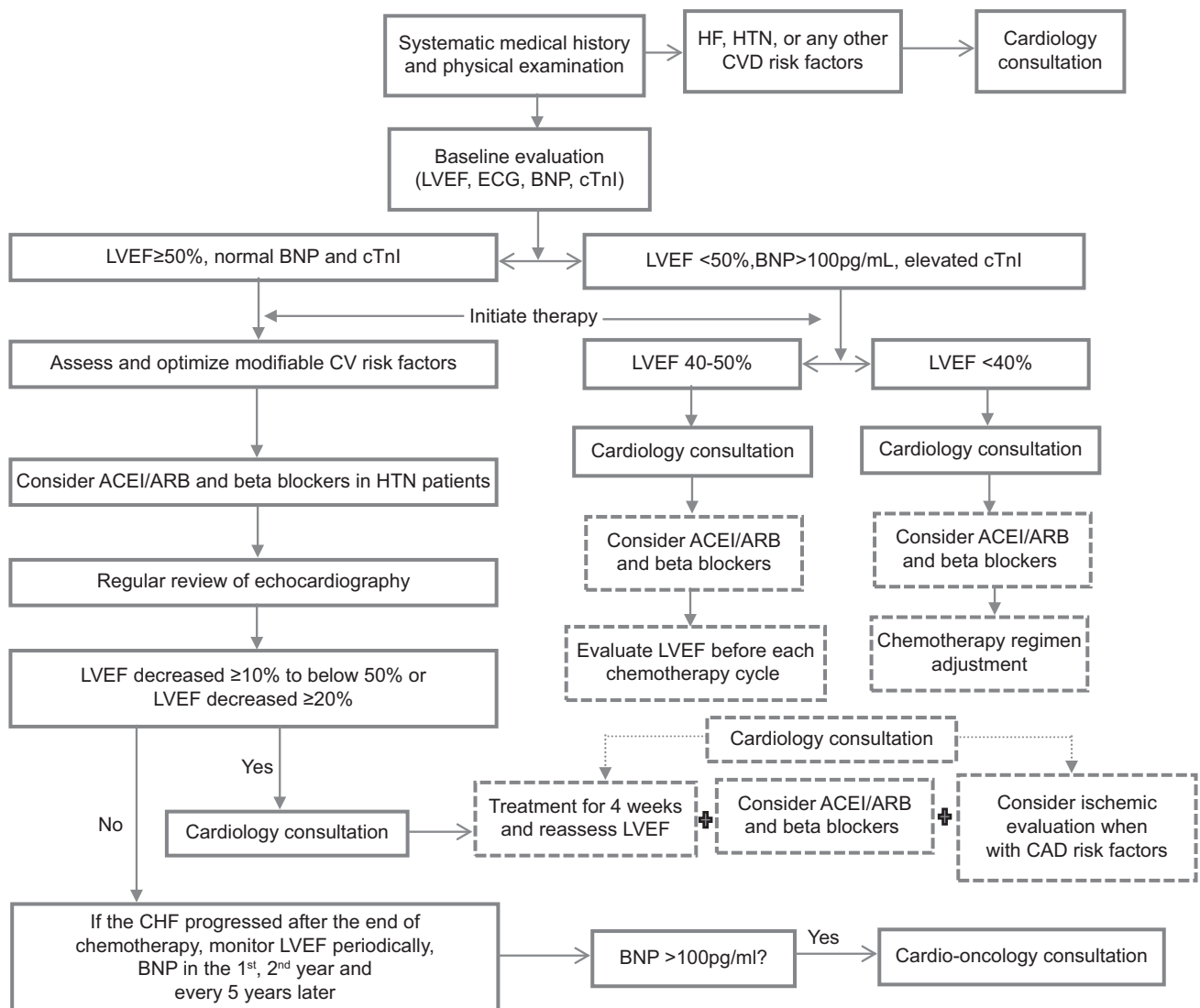
After the workshops, the expert panel published a proposal to call attention to the cardio-oncology and strengthened

physicians' education through national medical meetings and online promotion and established international exchanges and cooperation. The first cardio-oncology clinic in China was established in the First Affiliated Hospital of Dalian Medical University in August 22, 2016, and a preliminary cardio-oncology consultation program was performed simultaneously [Figure 1]. Some cancer centers also set up cardiology department to provide CVD care for cancer patients after the cardio-oncology workshops.

The First China Cardio-Oncology Conference entitled "Prevention, Early Intervention, Multidisciplinary Collaboration" was successfully held in Dalian on November 18–19, 2016. Meeting topics included the current status and future directions of cardio-oncology, overview of anticancer therapies and associated cardiotoxicity, establishment of cardio-oncology units in domestic hospitals, echocardiographic evaluation, cardiac tumors,

basic research, and case presentations. It attracted over 300 attendees from around the country, indicating the increased clinician awareness on the educational initiatives and the importance of this new discipline. Subsequently, numerous cardio-oncology forums were set up in academic conferences on cardiovascular and oncology for communication and education.

In addition, it is encouraging that the research work on cardio-oncology in China has achieved progression both in basic and clinical research. For example, further understanding on the relationship between end-stage carcinoma and acquired long QT syndrome might provide a new predictor of risk of all-cause mortality for cancer patients,<sup>[29]</sup> and we speculate that correction of the related risk factors will improve the prognosis of cancer patients. Animal experiments have explored potential specific protection measure against doxorubicin-induced



**Figure 1:** The cardio-oncology consultation program for cancer patients of the First Affiliated Hospital of Dalian Medical University. ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor antagonist; BNP: Brain natriuretic peptide; CAD: Coronary artery disease; CVD: Cardiovascular disease; cTnI: Cardiac troponin I; ECG: Electrocardiogram; HF: Heart failure; HTN: Hypertension; LVEF: Left ventricular ejection fraction.

myocardial dysfunction.<sup>[30]</sup> The booming development of cardio-oncology in China has beyond our expectation.

Although the cardio-oncology is rapidly growing in China, there are few Chinese cardio-oncologists because of the complexity of cancer and anticancer therapy and insufficient communication between cardiology and oncology before the recognition of cardio-oncology as an established and recognized specialty. A cardio-oncologist should be a health-care provider who is focused on the prevention, early detection, and management and treatment of cardiac injury that may stem from cancer or cancer therapies.<sup>[31]</sup> To develop the discipline, we need to first establish a training system based on the experience from Europe and America. The training curriculum should be targeted to cardiologists and focused on cancer and anticancer treatments as well as the associated cardiotoxicity.<sup>[32]</sup> It is important to increase our collective understanding and ability to modify the interactions between cancer and cardiovascular health.

The main focus of cardio-oncology is to improve the prognosis of cancer patients. The cardio-oncology specialty is at its infant stage in China. Currently, the lack of evidence to guide clinical decision-making and recommendations suitable for Chinese patients in cardio-oncology is a major challenge for health-care professionals. Several studies suggest that early detection of cardiovascular toxicity is possible through risk stratification before initiation of cancer therapy and periodic evaluation with physical examinations, echocardiography, magnetic resonance imaging, multigated acquisition scan, electrocardiogram, and biomarkers. ACEI/ARB and beta-blockers can reduce cancer therapy-related cardiac dysfunction and reduce mortality. The Society for Cardiovascular Angiography and Interventions recommends prechemotherapy cardioprotection. For patients with established CAD and without contraindications, adding or continuing ACEI and beta-blockers (preferably carvedilol or nebivolol) may provide additional cardioprotection. Based on the current experience, multicenter and multidiscipline association is optimal to create the clinical database and implement large prospective studies to develop the standard programs for CVD screening, prevention, treatment, and management.

The mechanisms of cancer and anticancer treatment-related cardiovascular toxicity are not very well studied. Basic, translational, and clinical research is needed to explore the molecular pathways of the CV toxicity from cancer therapies and to improve the effective interventions.

In summary, cardio-oncology is a new cross-discipline specialty with a focus on the cardiovascular health of cancer patients and cancer survivors. With the increasing recognition and the support of numerous cardiologists, oncologists, hematologists, cardiac imaging specialists, and basic research scientists, cardio-oncology has been steadily gaining attention in China. In addition to establishing multidiscipline training programs for cardiologists specializing in cardio-oncology, clinical and basic medical

research will be urgently needed to provide clinical data and evidence-based approach in cardiovascular care unique to Chinese patients with cancer.

*Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.*

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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**Supplementary Table 1: Incidence of common cardiovascular side effects associated with chemotherapy drugs**

<b>Chemotherapy agents</b>	<b>Left ventricular dysfunction (%)</b>	<b>Myocardial ischemia (%)</b>	<b>Hypertension (%)</b>	<b>Increase in QTc &gt;60 ms (%)</b>
<b>Anthracyclines</b>				
Doxorubicin (Adriamycin)		NA	NA	11–14
400 mg/m <sup>2</sup>	3–5			
550 mg/m <sup>2</sup>	7–25			
700 mg/m <sup>2</sup>	18–48			
Idarubicin (>90 mg/m <sup>2</sup> )	5–18	NA	NA	NA
Epirubicin (>900 mg/m <sup>2</sup> )	0.9–11.4	NA	NA	NA
Mitoxantrone (>120 mg/m <sup>2</sup> )	2.6	NA	NA	NA
<b>Alkylating agents</b>				
Cyclophosphamide	7–28	NA	NA	NA
Cisplatin	NA	0.2–12	NA	NA
<b>Antimetabolites</b>				
Clofarabine	27	NA	NA	NA
<b>Antimicrotubule agents</b>				
Paclitaxel	<1	0.2–4	NA	NA
<b>Monoclonal antibodies</b>				
Trastuzumab	1.7–20.1	NA	NA	NA
Bevacizumab	1.6–4	1–6	23.6	NA
<b>Small molecule tyrosine kinase inhibitors</b>				
Axitinib	NA	NA	40.1	NA
Sunitinib	2.7–19	1–13	21.6	
Vandetanib	NA	NA	24.2	12–15
Pazopanib	7–11	2–10	NA	NA
Sorafenib	4–8	1–2	15.3	NA
<b>Others</b>				
Arsenic trioxide	NA	NA	NA	35

NA: Not available.