

## Chemoradiotherapy-Associated Cardiovascular Toxicity: A Need of Cardio-Oncology to Improve

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### Abstract

Cancers and cardiovascular diseases are the leading causes of death among humans. Given the increasing armamentarium of cancer treatments with a potential for cardiovascular toxicity, cytotoxic and molecularly targeted drugs, radiation-associated cardiovascular toxicity is an increasing problem both for both the oncologist and cardiologist, which suggests a need for cardio-oncology (or onco-cardiology) to minimize the knowledge gap between these fields and to determine the best strategies to help recognize, detect, treat, prevent, and predict these adverse cardiovascular events. In this review, we will briefly discuss the cytotoxic anti-neoplastic and targeted drugs and various radiation-induced cardiovascular diseases with their potential mechanisms, and strategies for treatment, monitoring, and detection.

**Keywords:** Cancer; Cardiovascular disease; Chemotherapy; Radiotherapy; Targeted drugs

### Introduction

Cancer, cardiovascular disease (CVD), chronic respiratory disease, and diabetes are the four main types of non-communicable chronic diseases [1]. Globally, the burden of malignancies and CVDs is increasing, partially due to common risk factors such as smoking. It was estimated that approximately 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008 [1,2]. Worldwide, thoracic malignancies, including primary cancers of the lung and esophagus, accounted for 21.5% of all cancers (excluding skin cancer) among men, and malignancies arising in the breast, lung, and esophagus accounted for 31.4% of all cancers among women [2]. Approximately 30% of global cancer deaths in men were due to primary lung and esophageal carcinomas, and in women were due to breast, lung, and esophageal cancers [2]. Although the cancer spectrum differs between developed and developing countries, the estimated new cases and cancer deaths from thoracic malignancies in developing countries such as China, proportionally resembled those of developed countries [2]. Both the local and systemic therapy used to treat these thoracic tumors can result in direct or indirect damage to the heart and its substructures, and therefore may lead to cancer therapy-associated cardiovascular toxicities (CTACVT).

With the increasing availability of new anti-cancer drugs and improvement in advanced radiation techniques, there was an increase in long-term cancer survivors with various malignancies [3,4]. However, a recent study showed that the risk factors for CVD are common among long-term survivors and may compromise the long-term health [5]. The cumulative incidence of CTACVT after adjuvant breast cancer therapies may be as high as 33%, which suggest that anti-cancer treatment may directly result in cardiac diseases, accelerate

occult CVD, or increase the risk of CVD [6]. Therefore, oncologists and cardiologists should work together, prior to initiation of cancer therapy, to deliver optimal survivorship care that addresses both tumor control and CVD risk factors [5]. As such, cardio-oncology (or onco-cardiology), as a novel discipline, may prove beneficial in the optimization of anti-cancer and cardiovascular treatment.

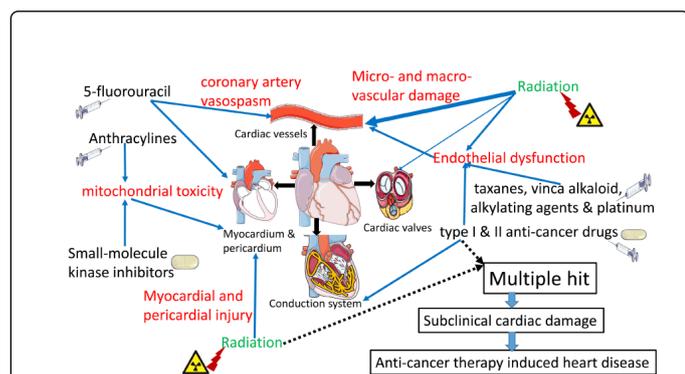
The aim of cardio-oncology, an interdisciplinary field between cardiology and oncology, is to investigate the mechanisms of CTACVT, conceive innovative strategies, gather data to enhance evidence-based approaches, develop interdisciplinary expertise, maximize correct clinical administration, and optimize therapeutic opportunities with minimal unfavorable effect on the prognosis of patients with these two concomitant diseases [7]. Several large centers specializing in cancer treatment have already established an integrated cardiology unit, such as the MD Anderson (Houston) and Memorial Sloan-Kettering cancer center (New York) in the USA and the European Institute of Oncology in Milan, Italy [7,8]. In this paper, we will briefly discuss the evidence and possible mechanisms of CTACVT, especially for CVDs that occur long after anti-cancer drugs and/or radiation therapy, and some strategies for enhancing awareness, early recognition and detection, prevention, treatment, and prediction of CTACVT, which will benefit to the oncologists and cardiologists, as well as their patients.

### Cancer Therapy-Associated Cardiovascular Toxicity

Surgery, radiation therapy, and drugs, including cytotoxic and targeted agents, are the main modalities for the treatment of cancer. Despite the emergence of anti-cancer drugs with less toxicities and improvement in radiation techniques, the cardiovascular toxicity resulting from treatment should not be neglected because of the additional risk to cancer survivors and potential deterioration in their quality of life. In this section, we will briefly discuss the anti-cancer drug and radiation-induced cardiac and vascular toxicities.

**Drug-Associated Cardiovascular Toxicities:** Chemotherapeutic agents and/or molecularly targeted drugs are widely used in the treatment of various malignancies [9]. Anti-cancer drug-associated cardiovascular toxicity is of increasing concern, which highlights the need to comprehensively consider the long-term effect on patients who receive anticancer treatment with various drugs [10-14]. Classic cytotoxic and molecularly targeted drugs are the two main forms of systemic anti-cancer agents presently used. Majority of these drugs may result in severe adverse cardiovascular effects such as heart failure (HF), left ventricular dysfunction, myocardial ischemia or infraction, hypertension, arrhythmias, and pulmonary arterial hypertension [10].

Anti-cancer drugs may cause reversible and/or irreversible damage to cardiac and/or vascular structures. The classic chemotherapeutic drugs such as anthracyclines, 5-fluorouracil, etc. is classified as type I anti-cancer drugs that might induce the irreversible cardiovascular damage, and the molecularly targeted drugs such as trastuzumab, erlotinib are the type II agents that cause to the reversible cardiovascular dysfunction [15]. Despite their limitations and relative arbitrariness, anticancer drugs can be categorized as type I and type II agents based on these toxicities [12]. The various CTACVT and their possible mechanisms are summarized in Table 1.



**Figure 1:** An outline of how anti-cancer therapy-related cardiac damage could theoretically combine to cause various cardiovascular toxicities. Cytotoxic such as anthracyclines, 5-fluorouracil, etc., molecularly targeted drugs and radiation might damage directly or indirectly to the cardiac vessels, valves, conduction system, myocytes and pericardium. The red words indicate their possible mechanisms that induced cardiovascular toxicities (as indicated in narrow solid arrow). The combination of various anti-cancer agents or of anti-cancer drugs with radiation might interact via multiple hit hypothesis (as indicated in dashed arrow) to accelerate cardiovascular toxicities and gradually result in various subclinical or clinical chemoradiotherapy-related heart diseases. Generally, type I anti-cancer drugs mainly include the classic cytotoxic drugs such as anthracyclines, 5-fluorouracil and so on that could cause to the irreversible cardiovascular damage. And majority of type II agents are molecularly targeted drugs such as trastuzumab, erlotinib, etc. that might result in the reversible cardiovascular dysfunction.

The precise pathogenesis of CTACVT has not yet to be fully elucidated and is outlined in Figure 1. Anthracyclines are widely used in the treatment of cancers such as breast cancer, lymphoma, and sarcoma, and their CTACVTs are of growing concern [16]. Anthracycline-associated cardiac toxicity mainly included HF,

decreased left ventricular ejection fraction (LVEF). Doxorubicin-induced HF is related to the cumulative dose. The prevalence of HF was estimated to be 0.2% for a cumulative dose of 150 mg/m<sup>2</sup> and 8.7% for a cumulative dose of 600 mg/m<sup>2</sup> [17]. Doxorubicin-associated cardiac toxicity may result from the impaired cardiac oxidative phosphorylation caused by mitochondrial dysfunction. All anthracyclines are converted to secondary alcohol metabolites that are not completely cleared and increasingly accumulate in the cardiomyocytes. These secondary metabolites have a considerably higher potency than the anthracyclines themselves, in terms of inactivating Ca<sup>2+</sup>-handling proteins of the contraction-relaxation cycle [18]. Available data seem to support the theory of coronary artery vasospasm as a pivotal contributor to 5-fluorouracil (5-FU)-induced cardiovascular toxicity [19]. Drug-induced endothelial dysfunction may be a possible mechanism for other anticancer drugs such as taxanes, vinca alkaloid, alkylating agents, and platinum, as shown in Table 1.

Although the wide use of small-molecule kinase inhibitors such as sunitinib and imatinib, and antibody-based cancer signaling pathways blockers provides enormous benefit to cancer patients and has had a major impact on their long-term survival, they carry the risk of cardiovascular toxicities, and available data have indicated that these agents adversely affect cardiac function in a subset of individuals [20]. Several kinases localize to the mitochondria and regulate mitochondrial function, and small-molecule kinase inhibitor-induced mitochondrial toxicity can be evoked via inhibition of numerous mitochondrial processes including biogenesis, substrate oxidation, and oxidative phosphorylation [20]. However, many cardiac events were not anticipated based on preclinical safety evaluation, and a majority of the underlying molecular events remains to be addressed by further studies.

Nowadays, many chemotherapeutic regimens include a combination of two or more (typically cytotoxic and/or targeted) drugs. For example, anthracyclines, taxanes, and/or trastuzumab are frequently used as the first-line and salvage treatments for patients with HER-2+ breast cancer [21]. In preclinical settings, toxicity and safety were evaluated using various pharmacological models. In clinical settings, however, these drugs are no longer administered alone, suggesting the need for a “multiple-hit hypothesis” when investigating toxicity, interpatient variability, and their potential mechanisms under multi-drug exposure [18].

**Radiation-Associated Cardiovascular Toxicities:** Radiation, an important modality for local treatment, may cause non-specific damage to the heart and cardiac substructures. Radiation-associated heart diseases mainly include four conditions: pericarditis, pericardial fibrosis, diffuse myocardial fibrosis, and coronary artery disease (CAD) [22]. Although the incidence may be lower with the use of modern techniques, the estimated incidence of radiation-induced cardiac disease is 10-30% during the 5-10 years post-treatment [23]. One thousand four hundred and seventy four survivors of Hodgkin’s lymphoma (HL) were retrospectively analysed (median follow-up duration, 18.7 years) to estimate the risk of myocardial infraction and HF. The results showed that compared with the general population, there was a 3-5-fold increase in the incidence of several CVDs, and 66-80% of all CVDs in the treated population resulted from HL treatment [24]. A meta-analysis showed that mortality from heart disease was increased by 27% in women who were randomized to surgery and postoperative radiotherapy compared with that in women who were randomized to surgery alone [25]. In patients with testicular cancer

who received radiotherapy and chemotherapy, the risk of CVD increased 1.5-3.7-fold compared with that in the general population, especially in those who received mediastinal radiation [26]. A population-based case-control study of major coronary events, including myocardial infarction, coronary revascularization, and death from ischemic heart disease, indicated that the rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy with no apparent threshold, and the increased risk persisted more than two decades after radiotherapy [27]. The risk of heart disease among atomic bomb survivors increased by 14% per Gy, although it is

uncertain if risk was elevated for exposures <0.5 Gy [28]. The pathogenesis of myocardial ischemia after radiation may result from acceleration of age-related atherosclerosis caused by macro-vascular injury. This can lead to coronary artery disease several years or decades later, although micro-vascular injury reduces capillary density that can become apparent within months [22]. Additionally, radiotherapy itself has a considerable effect on the local micro-environment and endothelial cells, which may also contribute to radiation-induced damage [29].

Chemotherapeutics	Example of drugs	Cardiovascular damage	Potential mechanisms
<b>Type I agents</b>			
Anthracyclines and analogues [12,16]	Doxorubicin, epirubicin, mitoxantron	HF (0.2-8.7%), Left ventricle dysfunction, Acute myocarditis, Arrhythmia	Cardiomyocyte death via necrosis or apoptosis
Antimetabolic drugs [12,19]	5-Fluorouracil, capecitabine, cytarabine	Angina, Arrhythmia Myocardial infarction, HF, Sudden death, Cardiomyopathy, Myopericarditis, Cardiogenic shock, 5-FU prolonged infusion regimens (7.6–18%), Shorter bolus regimens (1.2–3.0%)	Coronary artery spasm, Myocardial damage, Endothelial dysfunction, Thrombogenic effects or thrombus formation, Myocardial necrosis, Accumulation of metabolites
Taxanes [11]	Paclitaxel, docetaxel	HF, Myocardial ischemia, LVD, Arrhythmia	Damage to Cardiomyocytes, Endothelial dysfunction,
Vinca alkaloid [11]	Vinblastine, vincristine, vindesine, vinorelbine	Myocardial ischemia, LVD, Arrhythmia	Endothelial dysfunction, Cell signaling/survival block
Alkylating agents [12]	Cyclophosphamide, ifosfamide	LVD (7–28%), Pericardial effusions, Perimyocarditis	
Platins [11,65]	Cisplatin, carboplatin,	Myocardial ischemia, Stroke, Vascular thrombosis	Endothelial dysfunction
<b>Type II agents</b>			
Antibodies	Trastuzumab [73,74]	HF (0.5–4.0%), LVD (1–30%), Arrhythmia (2–8%), Myocardial infarction (1%), Cardiac death (<0.1%), Tricuspid regurgitation (1%)	Endothelial dysfunction
	Bevacizumab[75]	Hypertension (20.0–26.0%), Thromboembolism (<1.0–1.9%), LVD (<1.0–2.2%)	Endothelial dysfunction, Vasoconstriction, Vascular rarefaction
Tyrosine kinase inhibitors(TKI)	Imatinib[20]	Hypertension, HF or LVD (0.5–1.7%), Angioedema,	NA
	Sorafenib, Sunitibib [75]	Hypertension (10.4–24.0%), LVD (1–11%), Thromboembolism (<1.0–1.7%)	Myocardial depletion, Hypertrophy;
Thalidomide and analogs [76]	Thalidomidelenalidomide	Venous thromboembolism (26%), Stroke, Myocardial infarction	Angiogenesis inhibition Endothelial dysfunction
COX-2 specific inhibitors (-coxib) [77-79]	Celecoxib, rofecoxib	Cardiovascular thrombotic events (2.3–3.4%), Myocardial infarction, Heart failure, Stroke	Thrombosis Vasoconstriction
Selective estrogen receptor modulators (SERM)[80]	Tamoxifen, anastrozole,	Cardiovascular Disease (3.4–4.2%),	NA

	letrozole, exemestane	Cerebrovascular Disease (1.4–1.5%), Venous Thrombosis (1.6–2.8%)	
Anti-androgen drugs [81,82]	Leuprolide, goserelin, flutamide	Total cardiovascular events (7.1–11.2%): Acute coronary syndrome (2%), Thromboembolic stroke (1%), Venous thromboembolism (3%), Lipid and glucose metabolic dysfunction	NA

**Table 1:** The different manifestations of CTACVT by anticancer agents and possible mechanisms for the associated toxicity

**Abbreviations:** CTACVT: Cancer Therapy Associated Cardiovascular Toxicity; HF: Heart Failure; LVD: Left Ventricle Dysfunction; COX-2: Cyclooxygenase-2; NA: Related Mechanism is Unknown

The numbers in parenthesis indicate the estimated incidence available in the literature.

### Types of CTACVT

**Definition of CTACVT:** Cardiac disorders in the Common Terminology Criteria for Adverse Events version 4.0, mainly include various arrhythmias, acute coronary syndrome, cardiac chest pain or palpitations, myocardial infarction, cardiac arrest, heart failure, left or right ventricular dysfunction, pericarditis, myocarditis, cardiomyopathy, cardiac valve disease, and pericardial effusion/cardiac tamponade and the vascular disorders mainly include hyper/hypotension, thromboembolic events, peripheral/visceral ischemia, lymphedema, and vasculitis or phlebitis [30]. Acute coronary syndrome is characterized by signs and symptoms related to acute ischemia of the myocardium secondary to coronary artery disease, and the clinical presentation covers a spectrum of heart diseases from unstable angina to myocardial infarction [30].

Heart Failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood and most patients with HF have symptoms due to impaired left ventricular (LV) myocardial function [31]. More than a decade of years ago, an independent cardiac review and evaluation committee has established criteria for the preliminary diagnosis of HF and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) recently updated the guideline for the management of heart failure [31,32]. Though Ejection fraction (EF) values are dependent on the imaging technique used, method of analysis, and operator, it is considered important in classification of patients with HF [31]. ACCF/AHA recommended that patients with HF were consistently classified into HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF). HFrEF (also referred to as systolic HF) is defined as the clinical diagnosis of HF and EF≤40%. The diagnosis of HFpEF (also referred to as diastolic HF) as EF 50% is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF and there is, to date, no efficacious therapies. When the EF ranged 41% from 49%, these patients fall into a borderline or intermediate group. For a subset of patients with HFpEF who previously had HFrEF, these patients with improvement or recovery in EF > 10% was defined as improved group and they may be clinically distinct from those with persistently preserved or reduced EF [31]. Both the ACCF/AHA stages of HF and the New York Heart Association (NYHA) functional classification

provide useful and complementary information about the presence and severity of HF [31,33].

Heart failure associated with cancer treatment can be an acute, subacute, or chronic side effect. Acute or subacute cardiovascular toxicity frequently occurs any time from the initiation of therapy to 2 weeks after treatment completion. For example, these toxicities include acute coronary syndrome, alteration in myocardial function or pericardium, various arrhythmias, and abnormalities in ventricular repolarization. Chronic cardiovascular toxicity is arbitrarily divided into early and late adverse effects according to the time of appearance. Normally, early chronic toxicity appears within 1 year after treatment completion and late chronic toxicity occurs >1 year after treatment completion [12].

**Types of Cardiovascular Toxicities:** Although a single anti-cancer drug can cause a number of cardiac diseases, CTACVT is generally divided into seven categories: cardiac dysfunction, cardiac ischemia, hypertension, arrhythmia, pericardial disease, cardiac valvular disease, and thrombotic events. In this section, we will briefly discuss these different categories of CTACVT.

**Cardiac Dysfunction:** In terms of CTACVT, cardiac dysfunction usually includes decreased LVEF, left ventricular dysfunction (LVD), or HF although they may be the end of disease course for myocarditis, pericarditis, myocardial infarction, and cardiomyopathy [34]. Majority of type I anticancer drugs cause cardiac dysfunction (Table 1). HF is the dose-limiting toxicity for anthracyclines, especially doxorubicin and epirubicin. Usually, decreased LVEF precedes cardiac dysfunction without symptoms. Then, with an increasing cumulative dose of anthracycline, LVEF gradually deteriorates causing more severe complications such as LVD and HF. However, if discontinuation of anthracycline at the low or moderate cumulative dose decreases LVEF (a decrease in the LVEF by >15% to an absolute LVEF of 30-45%), the LVEF may stabilize without deterioration [16]. The reported incidence of 5-FU-associated cardiotoxicities ranges from 1.2% to 18% [19]. Although changes due to myocardial ischemia from a coronary vasospasm with a nonspecific electrocardiogram (ECG) tend to occur most commonly during the first cycle of administration with a median time to symptom onset of 12 h (range: 3-18 h) following initiation of infusion, the absolute incidence of LVD and HF is considerably low [19]. It should be noted that a single type I anticancer drug such as doxorubicin, may result in systolic and/or diastolic cardiac dysfunction with or without symptoms due to a number of mechanisms, including elevated calcium ion (Ca<sup>2+</sup>) concentration, left ventricular wall stiffness, reduced expression, increased disorganization of myofibrils, induction of apoptosis, and left ventricular hypertrophy [18]. Similarly, the prevalence of cardiac dysfunction from the other type I drugs such as taxanes and platins,

was very low, and the precise pathogenesis has yet to be fully elucidated.

**Cardiac Ischemia:** Although rare, antimetabolic drugs such as 5-FU, taxanes, vinca alkaloids, platins, and COX-2 specific inhibitors, may cause cardiac ischemia, as shown in Table 1. The reported ischemic cardiac events resulting from 5-FU administration mainly include angina and myocardial infarction [19]. The proposed mechanisms of 5-FU-induced cardiac ischemia are coronary artery spasms and endothelial damage [19]. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), improved outcomes when combined with chemotherapy regimens. Bevacizumab has occasionally been associated with myocardial infarction in 0.6-1.5% of patients [35]. Patients who receive thoracic radiation have a higher risk of cardiac mortality and morbidity, in which ischemic events, including coronary artery disease and myocardial infarction, were caused by direct damage to the coronary artery and its endothelial cells [22]. However, the synergism between radiation and anticancer drugs remains uncertain.

**Hypertension:** Hypertension is one of the most common comorbid conditions in cancer patients, and some the antiangiogenic cancer drugs such as bevacizumab, sorafenib, sunitinib, axitinib, and vatalanib, etc. can induce or exacerbate hypertension [36]. Its incidence ranged from 2.0% to 35.9% for all grades of toxicity and did from 0% to 20.5% for grade 3 or 4 [36]. In a recent randomized phase III trial, for patients with advanced renal cell carcinoma who received axitinib or sorafenib, treatment-emergent all-causality hypertension occurred in 40.4 % (145/359) and 29.0% (103/355) in axitinib- and sorafenib-treated patients respectively, with grade 3 hypertension reported 15.3% and 10.7% respectively, and the incidence of grade 4 hypertension was reported in 0.3% in each group [37]. Possible mechanisms of angiogenic inhibitor-induced hypertension include the decreased VEGF expression or activity (which contributes to the increase of systemic vascular resistance and the leading to thrombotic microangiopathy), vascular rarefaction, down-regulation of nitric oxide production, and dysregulation of renal endothelial cells [36]. Pre-existing hypertension is an important risk factor for severe hypertensive sequelae in cancer patients following anticancer treatment [38].

**Arrhythmia:** The overall incidence of arrhythmias in patients receiving anticancer treatment is unclear and varies with different treatment regimens. The majority of type I drugs and some type II agents such as monoclonal antibodies, may induce various cardiac arrhythmias, as shown in Table 1. The clinical manifestations of cardiac arrhythmias associated with anticancer agents are diverse and can range from acutely induced cardiac arrhythmias to Q-T interval prolongation. Atrial fibrillation is the most prevalent arrhythmia in cancer patients with an incidence of up to 12.6%, and is responsible for significant morbidity following cancer surgery. Many anticancer agents such as anthracyclines, anti-microtubule agents, antimetabolites, alkylating agents (cisplatin and cyclophosphamide), tyrosine kinase inhibitors, arsenic trioxide, thalidomide, and interleukin-2, are known to cause arrhythmias [39]. The risk factors include advanced age, cardiac irradiation, the presence of amyloid infiltration, and any underlying conduction system disturbance, as well as the cancer itself [38]. Interleukin-2 administration is associated with enhanced capillary permeability and intravascular volume depletion, which may be associated with a variety of supraventricular and ventricular arrhythmias in up to 10% of treated patients [40].

The identifiable and quantifiable Q-T interval prolongation, or “torsades de pointes,” can cause life-threatening cardiac arrhythmias [41]. Arsenic trioxide, anthracycline, tamoxifen, and serotonin-type-3 receptor antagonist might cause Q-T interval prolongation, and many risk factors, including sex, age, and abnormal baseline ECG, may be predictive of this side effect [42].

**Pericardial or Cardiac Valvular Disease:** Both pericardial and cardiac valvular diseases are relatively rare occurrences. Compared with anticancer drug-induced pericardial side effects, radiation-induced pericardial complications are more frequent. Radiation-related pericarditis usually manifests as a pericardial effusion and is characterized by an exudate of protein-rich fluid within the pericardial sac. Gradually, the fibrin in the exudate accumulates on the mesothelial lining of the epicardium or the parietal pericardium. This condition progresses to pericardial fibrosis because of collagen deposition, and is characterized by a thickened pericardium [22]. With the rapid improvement in radiation techniques and treatment strategies, the symptomatic radiation-related pericardial disease is seldom encountered in clinical settings. However, although rare, anticancer drugs such as alkylating agents may induce pericardial effusion and myopericarditis [12].

Anticancer drug-associated valvular heart disease usually manifests as a sequela of cardiomyopathy, LVD, or HF. Any resultant enlargement of the cardiac valvular endothelial damage could lead to cardiac valvular stenosis and regurgitation that mainly involve the mitral and aortic valves [12]. Evidence of radiation-related cardiac valvular disease is lacking, and the precise incidence is unknown.

**Thromboembolism:** Thromboembolism, which usually occurs in veins, is the second leading cause of death among cancer patients, and venous thromboembolism frequently includes deep vein thrombosis and pulmonary embolism [43]. Systemic chemotherapy (eg. alkylating agents), anti-angiogenic drugs (eg., bevacizumab), immunomodulatory agents (eg. thalidomide and lenalidomide), hormonal therapy, and other supportive measures (eg. erythropoiesis-stimulating agents) have been shown to increase thromboembolic risk [43]. Cancer-associated thrombosis is associated with increased morbidity and mortality [43]. The risk of symptomatic venous thromboembolism during the first cycle of chemotherapy can be predicted based on the site of cancer, platelet count, hemoglobin level, use of erythropoiesis-stimulating agents, leukocytes count, and body mass index [43].

As a possible mechanism driving anticancer drug-associated thromboembolism, chemotherapy-induced effects on the coagulation system can promote blood clotting in the vessels, which is a precursor to thrombosis and thromboembolic events [11]. Angiogenesis inhibitors and vascular disrupting agents might alter normal hemostasis, which results in the disruption of the function and integrity of the vascular endothelium. Alkylating agents such as cisplatin can trigger platelet aggregation, enhance thromboxane formation by platelets, and activate arachidonic acid pathways in platelets [44]. In addition, some anticancer drugs can modify the expression pattern of adhesion molecules and endothelial cells, including integrins and cadherins, leading to alterations in cell-cell and cell-matrix connections and endothelium integrity [11].

### Strategies for Minimizing CTACVT

**Eliminating the Knowledge Gap:** Reference oncologists and cardiologists should carefully consider the risks and benefits of

anticancer therapy in patients with pre-existing heart disease or related risk factors. This is especially important in the extended adjuvant setting, where predictive factors for treatment benefits are scarce, and the potential harm from ongoing antineoplastic therapy may outweigh any small reductions in the probability of tumour recurrence. Cancer patients frequently receive various anticancer treatments that could damage the cardiovascular system and increase the risk for various CVDs. Oncologists should be fully aware of the possible toxicities prior to administering anticancer therapy, and cardiologists should comprehensively consider all previous treatment-associated risks to the heart. However, there is a sizable knowledge gap between these specialties. Cardio-oncology can provide a knowledge-sharing platform between the oncology and cardiology communities and optimize treatment strategies. Moreover, major gaps exist in the knowledge of the precise mechanisms, prevalence, risk factors, early detection, predictive biomarkers, and evidence to guide the prevention and treatment of CTACVT, which should be the focus of future studies.

**Strategies to Limit CTACVT:** The management of CTACVT was highly recommended in the European Society of Medical Oncology clinical practice guidelines [12]. Strategies to reduce CTACVT should be based on the simple principle that therapeutic efficacy should not be compromised. For breast cancer patients, optimal chemotherapeutic combinations include trastuzumab without anthracyclines, short-term trastuzumab treatment or individualized anthracycline therapy that was selected based on the degree of expression of both the HER2 and TOP2A genes [35,45]. Optimizing the order of drug administration will likely benefit patients by reducing the cardiovascular toxicities. For example, pre-treatment with docetaxel 12 h before doxorubicin administration significantly reduced the incidence of doxorubicin-induced toxic deaths compared with the simultaneous dosing schedule [46]. Replacing rapid infusions with slow infusions may diminish the cardiac uptake of anthracyclines, resulting in decreased cardiac toxicities [18]. In addition, liposomal forms of doxorubicin, paclitaxel, and docetaxel have similar efficacy to that of conventional drugs with a significantly lower risk for cardiovascular toxicities [35,47,48].

Among breast cancer patients with left-sided tumors, irradiated women have a low frequency of comorbidity and higher relative incidence ratios for several different heart morbidities. These morbidities mainly include ischemic heart disease, in particular acute myocardial infarction and angina, which indicate that the coronary arteries, especially the left anterior descending coronary artery, may be the critical substructure for development of late radiation-induced heart morbidity [49]. Therefore, radiotherapy should be optimized in various aspects. Radiotherapy planning-related factors include the cardiac substructures, total dose and fractionation, and patient position during radiotherapy; the technique-related aspects involve the definition and dose/volume report of the cardiac organ at risk; and the endpoint-related aspects are the mortality, morbidity, sub-clinical heart disease, and the frequency of evaluation [49]. Since the precise dose/volume parameter for predicting the radiation-related cardiac events remains unknown, it may be prudent to minimize the radiation dose to all cardiac substructures, including the anterior myocardial territory that covers the myocardium and the coronary artery in the anterior rim or the heart [50-52]. In addition, the effects of both cardiac motion and set-up should be considered when estimating the radiation dose and in the estimation and report of dose-volume parameters in radiation planning [53]. Similarly, cardiac radiation dose or volume should be minimized during chemoradiotherapy in

lung cancer, esophageal cancer and Hodgkin's lymphoma [24,54,55]. The optimal strategies to limit the cardiac toxicities resulting from radiotherapy, chemotherapy, or targeted drugs are the topics that warrant further study.

**Monitoring of CTACVT:** The increased incidence of cardiac events among cancer survivors emphasizes the need for screening strategies to identify high-risk patients [23]. Monitoring of patients receiving anticancer therapy depends on various factors such as patient age, comorbidities, cumulative dose of drugs that can potentially damage the heart, radiation dose and volume to the cardiac substructures, and individual genetic susceptibility [35]. According to current guidelines for cardiovascular monitoring during and after systemic anticancer treatment, the cardiac function of breast cancer patients who receive anthracyclines and/or trastuzumab in the adjuvant setting should be monitored at baseline and every 2 years thereafter, and the usually recommended testing includes ECG and Doppler echocardiography with LVEF measurement [12]. The advantages and disadvantages of the standard methods used for monitoring cardiovascular toxicity in clinical practice are well-documented; these methods include echocardiography, radionuclide angiography, and electrocardiography [35]. Monitoring LVEF is the most common method used to screen for toxic effects on the heart with the disadvantage of underestimating cardiac damage [56]. Tissue Doppler imaging, stress echocardiography, scintigraphy, advanced magnetic resonance imaging, and computed tomography are all promising techniques for the monitoring and early detection of cardiovascular toxicities. Although the selection, frequency, and significance of these techniques in cardiovascular surveillance are unknown, optimization of monitoring and surveillance of cancer patients is essential for the early detection of the cardiotoxic effects of antineoplastic therapy [35].

**Management of CTACVT:** Angiotensin-converting-enzyme (ACE) inhibitors (e.g. enalapril) are recommended for the treatment of patients with subclinical cardiotoxicity induced by systemic anticancer drugs, and patients with LVD or HF should be treated according to the standard guideline-based heart failure therapy; patients should discuss the risks and benefits with the treating oncologist [57]. For patients with primary or secondary hypertension resulting from treatment with anticancer agents, antihypertensive drugs should be individualized to the clinical circumstances of the patient [58]. ACE inhibitors or angiotensin II receptor blockers are usually considered for patients with proteinuria, metabolic syndrome, or at high risk for chronic kidney disease. Treatment with non-dihydropyridine calcium channel blockers should be avoided in patients receiving CYP450 inhibitors, and dihydropyridine calcium channel blockers are preferred in elderly patients [63,59]. Low-molecular weight heparin is the recommended treatment for patients with newly diagnosed venous thromboembolism for a minimum of 3–6 months. Both drug-induced arrhythmia and radiation-associated heart diseases are usually treated as non-CTACVT [12,60].

**Prevention of CTACVT:** Late-onset cardiotoxicity usually develops over a period of months or years through asymptomatic cardiac dysfunction, which suggests that preventable drugs used to treat symptomatic events should be used earlier to prevent subclinical damage [18]. For example,  $\beta$ -blockers or angiotensin I-converting enzyme inhibitors are used to prevent systolic dysfunction induced by cumulative doses of anticancer agents. The dual mechanisms include the reduction in heart rate and afterload by these drugs, as well as shielding of endothelial cells from catecholamines or angiotensin II, rendering cardiomyocytes more resistant to hemodynamic and

chemical stress [57]. Statins (e.g., atorvastatin) with lipid lowering, anti-inflammatory, and antioxidant effects were used to prevent and treat atherosclerotic disease. The results of two clinical studies indicated that statins could preserve cardiac function by increasing LEVF and lowering the incidence of HF [57,61,62]. Dexrazoxane, a cardioprotective agent, is recommended for patients receiving >300 mg/m<sup>2</sup> doxorubicin who may benefit from continued doxorubicin-containing therapy, but not for routine use in breast cancer treatment with initial doxorubicin-based chemotherapy in the adjuvant or metastatic settings [63]. A recent meta-analysis regarding the role of cardio-protective therapy for prevention of cardiotoxicity caused by chemotherapy showed that prophylactic treatment with dexrazoxane, beta-blockers, statins, or angiotensin antagonists appears to have similar efficacy for reducing cardiotoxicity [64]. Recently, antioxidants such as vitamin E, selenium, lycopene, melatonin, resveratrol, and coenzyme Q10, have been identified as potentially beneficial cancer treatment agents because of their ability to inhibit oxidative injury caused by platinum-based compounds, but further studies are needed to confirm their role in the prevention of CTACVT [65].

**Predictive Biomarkers:** Biochemical biomarkers can be used as alternative diagnostic tools for the early detection of cardiovascular toxicity and the prediction of cardiac dysfunction [66]. Serological biomarkers for cardiovascular monitoring before, during, and after anti-tumor therapy include troponin, cardiac natriuretic peptide, and myeloperoxidase [11,66-69]. Troponin (including three isoforms: troponin C, troponin I, and troponin T) is a complex of three regulatory proteins that is integral to muscle contraction in the skeletal and cardiac muscles. Clinical evidence derived from previous studies indicates that troponin can be used to predict the occurrence, degree, and severity of LVD. Troponin levels can be used for the early detection of cardiotoxicity, before significant impairment of cardiac function. It also can cost-effectively discriminate patients who are at high-risk for cardiotoxicity from those at low-risk [66]. Cardiac natriuretic peptide has also been reported to have diagnostic and prognostic value with regard to CVDs, particularly HF [11,66]. Increased blood concentrations of B-type natriuretic peptide, a precursor of the cardiac natriuretic peptide, represent a pathophysiologic model of overload cardiomyopathy [66]. However, prospective studies are warranted to confirm the potential predictive value of cardiac natriuretic peptide concentrations in the blood to determine development of cardiac dysfunction [66]. Myeloperoxidase, a peroxidase enzyme most abundantly expressed in neutrophil granulocytes, contributes to the pathogenesis of anticancer agent-induced cardiovascular toxicity and may be a potential biomarker [70]. Multiple biomarkers such as troponin I, N-terminal pro-brain natriuretic peptide, cystatin C, and C-reactive protein, improved the prediction of cardiovascular-associated mortality [71]. However, the precise prediction value of the majority of these biomarkers needs to be validated in clinical settings.

## Conclusion

Malignancies and CVDs constitute two of the leading causes of death among humans. The majority of cancer patients receive antitumor treatment that can cause cardiovascular toxicity. Many cytotoxic chemotherapeutic agents and targeted drugs can result in a variety of CVDs that include decreased LEVF, LVD, HF, hypertension, myocardial ischemia, arrhythmias, and thromboembolism. Possible mechanisms involve direct or indirect drug-induced damage to the myocardium or endothelial cells of the coronary artery. Thoracic

radiation mainly causes damage to the ischemic heart, with the most reasonable explanation being that radiation-induced macrovascular injury accelerates age-related atherosclerosis and reduces capillary density. Cardio-oncology can provide a platform for oncologists and cardiologists that could minimize the knowledge gap between the two fields and optimize prevention and treatment strategies. Antineoplastic chemotherapy treatment regimens and radiation planning/techniques should be improved to limit cardiovascular toxicities. The majority of CTACVT are usually treated as non-cardiovascular toxicities. ECG, echocardiography, and cardiac biomarkers such as troponin, are frequently used for the monitoring, early detection, and prediction of CTACVT. Future studies should focus on the basic mechanisms of cardiovascular toxicities induced by anticancer treatment and strategies to minimize these unexpected complications. In addition, during the discovery of novel anticancer drugs with a potential for cardiotoxicity, both oncology and cardiovascular agencies need to work together to determine the optimal strategies for evaluation, surveillance, and reporting of adverse cardiovascular events that occur in preclinical and clinical settings [18,72].

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