Global Health & Medicine. 2021; 3(4):214-225.
REVIEW
DOI: 10.35772/ghm.2021.01024

Current status and future perspectives of onco-cardiology: Importance of early detection and intervention for cardiotoxicity, and cardiovascular complication of novel cancer treatment

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Abstract: The prognosis has improved remarkably in recent years with the development of cancer treatment. With the increase in the number of cancer survivors, complications of cardiovascular disease have become a problem. Therefore, the field of onco-cardiology has been attracting attention. The field of onco-cardiology covers a wide range of areas. In the past, cardiac dysfunction caused by cardiotoxic drug therapies such as doxorubicin (Adriamycin) was the most common cause of cardiac dysfunction, but nowadays, cardiovascular complications caused by aging cancer survivors, atherosclerotic disease in cardiovascular risk carriers, thromboembolism, and new drugs (*e.g.*, myocarditis caused by immune checkpoint inhibitors and hypertension caused by angiogenesis) are becoming more common. In this review, we summarize the latest findings of cardiotoxicity of cancer therapy, appropriate treatment and prevention, and cardiovascular complications of novel chemotherapy, which will increase in demand in the near future.

***Keywords*:** cardiotoxicity, anthracycline, immune checkpoint inhibitors-associated myocarditis, cancer-associated thrombosis (CAT), radiotherapy

Introduction

Because treatment for cancer has dramatically developed and prognosis has improved, cancer survivors have recently increased. While cancer is the leading cause of death, complications with the second leading cardiac disease are on the rise, and the need for management of cardiovascular complications in cancer survivors is increasing. Cancer treatment also has its characteristic side effects, and cardiovascular complications can be severe (*1*). Improvements in cancer have also led to an aging population of cancer patients and an increase in the number of cancer patients with cardiovascular risk. Now that reintegration into society after living with cancer is commonplace, there is a need to avoid the development of cardiovascular complications and interruption of cancer treatment. The relationship between cancer treatment and cardiovascular diseases/complications is receiving more and more attention, and the collaboration between oncologists and cardiologists is becoming more and more important.

The field of onco-cardiology was first featured in the 1960s when anthracyclines were used as a new cancer treatment. In the United States, the world's first onco-cardiology unit was established at MD Anderson in 2000. Barac *et al.* have presented the following roadmap (Figure 1) for the oncology and cardiology unit (*2*). Onco-cardiologists need to work seamlessly with cancer survivors, not only after cancer-associated heart disease has occurred, but also during the prevention phase of cancer development, treatment, and after cancer treatment has been completed.

In this review, we summarize the latest findings of cardiotoxicity for cancer therapy, appropriate treatment and prevention, and cardiovascular complications of novel chemotherapy, which will increase in demand in the near future.

Cardiac dysfunction and cardiovascular complications of chemotherapeutic drugs

Anthracycline-induced cardiotoxicity has been the most well known cardiac problem associated with cancer treatment. However, with the advent of molecularly targeted therapy and other advances in cancer treatment, new cancer treatment-related cardiovascular diseases have been reported. In addition to heart failure due to reduced cardiac function, vascular thromboembolism, such as myocardial infarction, and immune checkpoint inhibitor (ICI) -associated myocarditis have also been reported (*3*).

Cardiac dysfunction

Definitions of cardiac dysfunction

The most common cancer treatment-related cardiotoxicity is cardiac dysfunction resulting in heart failure. It is defined by the position paper from Europe Society of Cardiology (ESC) as the following: a decrease in left ventricular ejection fraction (LVEF) of at least 10% and LVEF less than 55% (*4*). The American Society of Echocardiography (ASE) has also defined the following: an LVEF of at least 10 percentage points below baseline and an LVEF of 53% or less (*5*), American Society of Clinical Oncology (ASCO) (*6*) and European Society of Medical Oncology (ESMO) (*7*) have also their own definitions (Table 1).

Cardiotoxicity from cancer treatment became of interest in the 1960s when anthracycline-induced cardiomyopathy was found as a fatal complication. In terms of whether cardiac dysfunction is reversible or not, they have been classically classified as Type 1 and Type 2 (*4,8*). Type 1 is dose-dependent and causes irreversible histological changes, as typified by anthracyclines; Type 2 is dose-independent and reversible. However, this classification is no longer used because drugs that are known to be reversible with type 2 are also irreversible in about 20% of cases (*8*). The latest guidelines of ASCO do not refer to them as Type I or II since the resulting cardiotoxicity/ myocardial dysfunction is more important than the mechanism of cardiotoxicity as a drug (*6*). Recently, tyrosine kinase inhibitors (*9*) and proteasome inhibitors (*10*) have also been reported to cause cardiomyopathy.

Clinical features and pathophysiology

For early detection of cardiovascular disease in cancer patients and the cardiovascular complications associated with cancer treatment, it is important to assess the patient's risk of cardiovascular complications prior to treatment. The traditional cardiovascular risk factors such as self-monitoring blood pressure, HbA1c and low-density lipoprotein (LDL) cholesterol levels, electrocardiography (ECG), and chest x-ray are important for this purpose. Patients at high risk need careful follow-up.

Careful daily physical examination is also important for early detection. The complaint of shortness of breath on exertion and chest pain, the findings of leg edema, and weight gain is checked at every visit. An

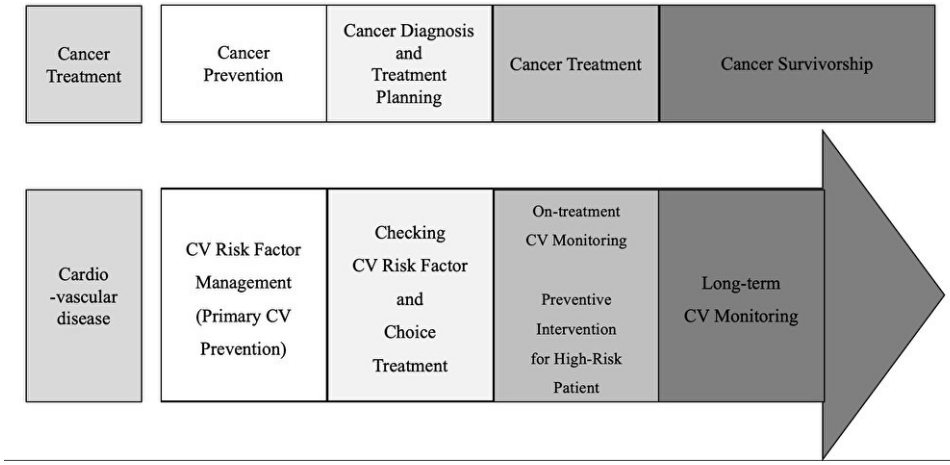

Figure 1. The roadmap for following the oncology and cardiology unit (*2*). Onco-cardiologists need to work seamlessly with cancer survivors, not only after cancer-associated heart disease has occurred, but also during the prevention phase of cancer development, treatment, and after cancer treatment has been completed.

Table 1. The definition of cancer treatment-related cardiotoxicity

	ASCO (*6*) Clinical practice guideline	ESMO (*7*) Clinical guideline	EACVI/ASE (*5*) Expert consensus	ESC (*4*) Position paper
Definition	An asymptomatic decrease in LVEF of 10% to less than 55% or a symptomatic decrease in LVEF of 5% to less than 55%	Decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of congestive heart failure, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symtoms	Decrease in the LVEF of > 10% points, to a value < 53%	LVEF: > 10% points decrease to a value below the lower limit of normality GLS: 15% relative percentage reduction from baseline

ASCO: American Society of Clinical Oncology; ASE: American Society of Echocardiography; EACVI: European Association for Cardiovascular Imaging; ESC: European Society of Cardiology; ESMO: European Society for Medical Oncology; GLS: Global Longitudinal Strain; LVEF: Left Ventricular Ejection Fraction.

arrhythmia is also checked by listening to the heartbeat and palpating the pulse. The abnormalities of ECG such as low voltage QRS potentials, ST changes, and QT prolongation may reflect cardiac dysfunction at a relatively early stage. It is still important to compare the results with those before treatment. A number of novel tyrosine kinase inhibitors, which have been used in cancer treatment, may cause QT prolongation and ECG should be checked (*11,12*). A chest x-ray is also used to check the cardiothoracic ratio and pleural effusion. Echocardiography is a very important and useful test. In general, decreased LVEF is an important finding, but is not suitable for early detection. The speckle tracking method used in echocardiography is a method that automatically tracks fine myocardial speckles using pattern matching to obtain coordinates (*13*). In particular, the left ventricular global long strain (GLS) obtained on the apical long-axis image is highly reproducible and can be useful for early diagnosis of disease and may be a prognostic factor (*5,14,15*). In high-risk patients, follow-up every 3 months is desirable (*16*). Either BNP or NT-proBNP in plasma may be useful as a biomarker for heart failure. Both BNP and NT-proBNP are elevated in advanced cardiac load and also useful in determining the response to treatment for cardiotoxicity (*4*). Troponin is a myocardial-specific marker that reflects myocardial damage and myocardial necrosis. Elevated troponin levels after the start of cancer treatment is predictive of a decrease of EF (*17*) and have been reported to be predictive of events such as cardiac death and heart failure (*18*). In any case, specific blood tests are recommended before cancer treatment and regularly when using potentially cardiotoxic drugs.

Anthracyclines

Anthracyclines act on nucleic acids regardless of what stage of the cell cycle and exert anti-tumor effects through DNA intercalation and inhibiting topoisomerase type II. Topoisomerase II is responsible for cleaving two strands of DNA. Doxorubicin forms a complex with topoisomerase type II and DNA expressed in cardiomyocytes, and the retention of DNA double-strand breaks cause cardiotoxicity (*19*). It is also reported to cause damage to the vascular endothelium (*20*). The frequency of doxorubicin increases with cumulative lifetime dose of 400 mg/m^2. For example, at a cumulative dose of 400 mg/m^2, the incidence of congestive heart failure is 5%, but above 700 mg/m^2, the incidence exceeds 48% (*21*).

The ASCO guidelines specify a high risk of cardiac dysfunction with anthracyclines use, and a high-risk group has been reported to have a cardiotoxicity risk even at doses below 250 mg/m^2 (*6*). The high-risk groups include the following: high-dose anthracyclines (> 250 mg/m^2), high-dose radiation (30 Gy) involving the heart in the field, having 2 or more cardiovascular risk factors such as smoking, hypertension, diabetes mellitus, dyslipidemia, or obesity, older age (> 60 years at the time of cancer treatment), decreasing cardiac function before or during treatment (LVEF50-55%, previous myocardial infarction, moderate or severe valvular disease), and sequential therapy with trastuzumab. Lyon *et al.* also stratified risk by history of cardiac disease, biomarkers, and risk of coronary disease (*22*). The time of onset of anthracycline cardiotoxicity has historically been classified as acute, early, and late (*23*). However, 98% of cases of cardiotoxicity now occur within the first year (*24*).

In particular, GLS on echocardiography is reported to detect cardiotoxicity at an early stage and should be checked frequently (*25*). Cardiac magnetic resonance imaging (CMR) has also been reported to provide early detection, especially T2 mapping, which is reported to be the earliest marker (*26,27*). It has also been reported that elevated troponin after the initiation of anthracyclines predicts left ventricular dysfunction and cardiac events (*17*).

HER2 inhibitors

HER2 is a receptor tyrosine kinase, which is involved in the regulation of cell proliferation, differentiation, migration, and survival (*28*). It is also involved in the development and maintenance of the nerves of the heart. In particular, trastuzumab is a key drug in HER2-positive breast cancer, and this drug has improved cancer prognosis (*29,30*). Trastuzumab is thought to increase the cardiotoxicity of anthracyclines, and Slamon *et al.* reported symptomatic or asymptomatic cardiac dysfunction was found in 27% of patients with the combination of anthracyclines and trastuzumab (*29*). In a 10-year follow-up of HER2-positive breast cancer, impaired cardiac function was 9.4% in the group assigned to a regimen containing paclitaxel, cyclophosphamide, and trastuzumab and 19.2% in the group assigned to an anthracycline-containing regimen (*31*). With paclitaxel plus trastuzumab, as the standard of care for HER2-positive early-stage breast cancer, heart failure is relatively rare, with Grade 3 or greater symptomatic heart failure reported in 0.5% and cardiac dysfunction in 3.2% of patients (*32*). The cardiotoxicity of trastuzumab is said to be reversible, but about one-third is reported to be prolonged (*8*). Pertuzumab is essentially a drug used in combination with trastuzumab; the Food and Drug Administration (FDA) recommends checking cardiac function every 3 months during treatment for recurrence and every 6 weeks for neoadjuvant chemotherapy. Lapatinib is used in combination with capecitabine in metastatic recurrent breast cancer. The incidence of cardiac events with lapatinib was as low as 1.6%, and mostly asymptomatic, with only a decrease in EF. Asymptomatic events were as low as 0.2% (*33*).

A pooled analysis (n = 1,961) of trastuzumab emtansine (T-DM1) showed some cardiac dysfunction

in 3.4% of patients (*34*). Trastuzumab-delux-Tecan caused 0.9% of patients to have impaired cardiac function (*35*). However, none of these patients have had much experience with the drug. The patients were already on trastuzumab for second-line use, and the use of anthracyclines should also be noted.

Vascular endothelial growth factor Inhibitors

Vascular endothelial growth factor (VEGF) has been identified as a factor that increases vascular permeability and causes angiogenesis (*36*). VEGF inhibitors improve the reach of antitumor drugs to cancer by blocking excessive VEGF signaling and normalizing tumor blood vessels, which are also highly permeable. VEGF inhibitors include the monoclonal antibodies bevacizumab and ramucirumab, as well as several other multi-kinase inhibitors that are used to treat a variety of cancers. VEGF is also thought to be important for tissue growth and angiogenesis in the heart; inhibition of VEGF is known to inhibit cardiac remodeling and cause heart failure. The most frequent cardiotoxicity is hypertension, but cardiac dysfunction is less common. In a large prospective observational study of breast cancer patients, bevacizumab caused left ventricular dysfunction in 2% of patients and symptomatic heart failure in 1% (*37*). With sunitinib, pazopanib, and axitinib, cardiac dysfunction was reported in 3 to 15% and symptomatic heart failure in 1 to 10% of patients (*4*). Risk factors include coronary artery disease, a history of valvular disease, and a history of anthracycline use.

Other tyrosine kinase inhibitors

The advent of tyrosine kinase inhibitors has dramatically improved the prognosis of chronic myeloid leukemia (*38*). For the cardiovascular system, ischemic heart disease and pulmonary hypertension have been reported as serious complications (*9*). There are few reports of cardiotoxicity with imatinib (*39*).

Treatment and prevention for cardiac dysfunction

Felker *et al.* reported that anthracycline-induced cardiomyopathy had a very poor prognosis, with a 2-year survival rate of 40% (*40*). A recent single-center report showed that with precise monitoring and appropriate early treatment when it occurred, the prognosis was no different than that of hereditary cardiomyopathy (*41*).

If symptomatic heart failure develops during chemotherapy, discontinuation of current chemotherapy should be considered. According to current heart failure guidelines, cardioprotective therapy such as using angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and beta-blockers, has been recommended, but there is no established evidence (*4,42*). The European Society for Medical Oncology (ESMO) guidelines for cardiac dysfunction caused by chemotherapy indicate a different response for type 1 and type 2 (*43*).

Only small reports of primary prevention have also been reported. In ACE inhibitors, patients with elevated troponin I immediately after initiation of high-dose adriamycin treatment divided into ACE inhibitor and non-ACE inhibitor groups, the ACE inhibitor group prevented the development of late cardiotoxicity (*44*).

In the beta-blocker group, Kalay *et al.* reported that prophylaxis by carvedilol prevented cardiac dysfunction in a small group of patients receiving anthracyclines (*45*). Avila *et al.* also reported that prophylaxis by carvedilol in patients scheduled to receive adriamycin prevented elevated troponin levels and diastolic dysfunction but did not change LVEF (*46*).

Some reports indicate an anti-inflammatory preventive effect of statins used for hyperlipidemia; Seicean *et al.* reported an association between statin use and the development of heart failure, although in a retrospective study (*47*). Although Vaduganathan *et al.* published a meta-analysis that the use of beta-blockers, ACE inhibitors, and ARBs was effective in primary prevention, heterogeneity and publication bias were noted and there still has been only limited evidence for these effects (*48*).

Dexrazoxane is a topoisomerase II beta inhibitor, intracellular iron chelator, and increases hypoxia-inducible transcription factors. It is expected to inhibit cardiomyocyte cell death and apoptosis, which is the basis for the development of cardiotoxicity, and has potential for a long-term protective effect against cardiotoxicity of anthracycline (*49*). Kalam *et al.* conducted a meta-analysis of 14 articles on prevention of heart failure, which also showed the efficacy of dexrazoxane, beta-blockers, ACE inhibitors, and statins (*50*). Further large, prospective, randomized trials are awaited (Table 2).

Immune checkpoint inhibitor (ICI) -associated myocarditis

ICIs are anti-tumor drugs with a new mechanism of action: by binding to immune checkpoint molecules such as PD-1 and CTLA-4, as well as to their co-receptor-binding ligands, they block inhibitory signals and enhance the immune response against cancer.

Since Brahmer *et al.* reported efficacy in non-small cell lung cancer (*51*), various trials have shown improved outcomes with the use of immune checkpoint inhibitors and in combination with other agents. The use of immune checkpoint inhibitors has been found to have characteristic side effects, such as the development or exacerbation of autoimmune and inflammatory diseases due to the loss of normal immune regulation (*52*). These immune-mediated side effects are called immune-related adverse events (irAEs). Cardiovascular complications such as vasculitis, arrhythmias,

Table 2. The summary of clinical studies of prevention of cardiotoxicity

Drug	Authors, Year (*Ref.*)	Type of Study	*n*	Target Group	Dose	Control Group	Follow-up Period	Outcome	Result (%)	*p*-value or Risk Ratio [95% CI]
ACE inhibitor	Cardinale, *et al.* 2006 (*44*)	RCT	56 *vs.* 58	Patients who showed a troponin I increase soon after high dose chemotherapy	Enalapril 20 mg/day	Not receiving ACE inhibitor	12 months	Absolute decrease > 10% units in rest LVEF associated with a decline below 50%	0 (0) *vs.* 25 (43)	< 0.001
Beta Blocker	Kalay N, *et al.* 2006 (*45*)	RCT	25/25	Patients whom antracycline therapy was planned	Carvedilol 12.5 mg/day	Placebo	6 months	LVEF	Carvedilol: 70.5 *vs.* 69.7 Placebo: 68.9 *vs.* 52.3 (baseline *vs.* follow)	Carvedilol: $p = 0.3$ Placebo: $p < 0.001$
Beta Blocker	Avila MS, *et al.* 2017 (*46*)	RCT	96/96	Patients with HER2-negative breast cancer tumor status and normal LVEF referred for anthracycline (240 mg/m^2)	Beginning with a dose of 3.125 mg twice a day, which was increased to 6.25 mg, then to a maximum dose of 25 mg	Placebo	6 months	Prevention of a ≥ 10% reduction in LVEF	14 (14.5) *vs.* 13 (13.5)	1.0
Dexrazoxane	Macedo AVS, *et al.* 2019 (*49*)	Meta-analysis	575/605	Patients with breast cancer receiving anthracycline with or without trastuzumab	1000 mg/m^2 or 10:1 or 20:1 (DEX : DOX) dose ratio	No therapy or Placebo	126 days to 5 years	Clinical heart failure	RR 0.19 [0.09 to 0.40]	< 0.001
Dexrazoxane	Macedo AVS, *et al.* 2019 (*49*)	Meta-analysis	383/1,414	Patients with breast cancer receiving anthracycline with or without trastuzumab	1000 mg/m^2 or 10:1 or 20:1 (DEX : DOX) dose ratio	No therapy or Placebo	126 days to 5 years	Cardiac events (Subclinical heart failure or admission due to cardiac causes)	RR 0.36 [0.27 to 0.49]	< 0.001

ACE: Angiotensin Converting Enzyme; CI: Confidence Interval; DEX: Dexrazoxane; DOX: Doxorubicin; LVEF: Left Ventricular Ejection Fraction; RCT: Randomized Control Trial; RR: Risk Ratio.

takotsubo-like syndrome, and pericardial disease have been reported, but the most common is autoimmune myocarditis (*53*). Johnson *et al.* reported a case of ICI-associated myocarditis in patients treated with nivolumab in combination with ipilimumab 12 and 15 days after treatment (*54*). Mahmood *et al.* reported that myocarditis occurred in 1.14% of patients at a median of 34 days and was more common in the combination group and in diabetes mellitus (*55*). Electrocardiographic changes were elevated in 89% of patients and troponin was elevated in 94% of cases. Hu *et al.* recommend checking baseline ECG and troponin before treatment and following up with troponin measurement every 4-6 weeks. If abnormalities are found, they recommend immediate ICI withdrawal and close examination, including echocardiography and CMR (*53*).

As for treatment, early initiation of high-dose steroids has been reported to improve prognosis (*53,55*). Zhang *et al.* reported an improved prognosis with early steroid pulse therapy in a retrospective study of 126 cases of myocarditis (*56*). Other high-dose therapies such as mycophenolate, infliximab, and anti-thymocyte globulin have been recommended as third-line treatment for steroid-refractory patients (*57*). In some cases of steroid refractory patients, abatacept, a CTLA-4 agonist, has been reported to be effective (*58*), but further clinical data are needed.

Ischemic heart disease

Ischemic heart disease (IHD) is the second leading cause of death after cancer. The number of cancer survivors is on the rise, as is the number of patients with cancer who are at risk for coronary artery disease due to an aging population. Factors such as smoking, diabetes, and obesity are also common risk factors for cancer patients and atherosclerotic atherothrombosis. Navi *et al.* reported a 2-3 times greater risk of myocardial infarction and cerebral infarction at 6 months after cancer diagnosis in cancer patients and non-cancer patients (*59*). With regard to therapeutic agents, 5-FU, widely used for gastrointestinal and gynecological cancers, had a 7.6% incidence of cardiovascular events and a 2.2% mortality rate at high doses (*60*). The mechanism may also involve endothelial damage and vasospasm (*61*). Cisplatin is an alkylating agent used in lung and gastrointestinal cancers. IHD is the most serious vascular hazard of cisplatin. The concomitant use of 5-FU increases the risk. The incidence of arterial thrombosis in patients treated with cisplatin-based chemotherapy was approximately 2% (*62*).

In recent years, particular attention has been paid to IHD caused by angiogenesis inhibitors such as anti-VEGF antibodies. The incidence of myocardial infarction has been reported to be 3.8% with bevacizumab (*4*). In a meta-analysis of 77 phase III RCTs, compared with non-users, arterial thrombosis (OR 1.52 [95% CI 1.17-1.98]), cardiac dysfunction (OR 1.35 [95% CI 1.06-1.70]), and myocardial ischemia (OR 2.83 [95% CI 1.72-4.65]) were found in the angiogenesis inhibitor group with VEGF inhibitors. Endothelial damage is thought to cause vasospasm and atherosclerotic collapse (*63*).

Hypertension

It is one of the most frequent problems in cancer treatment-related vascular disorders. Hypertension caused by VEGF inhibitors and multi-kinase inhibitors is typical. The frequency has been reported to be 11-45% (*4,64,65*). In a previous meta-analysis, VEGF inhibitor-induced hypertension was reported to have an OR of 5.28 [NNH 6] and severe hypertension to have an OR of 5.59 [NNH 17] (*66*). The mechanism in the acute phase is thought to be NO pathway inhibition by VEGF pathway inhibition and associated vasoconstriction (*67*). In the chronic phase, a decrease in vascular bed size and an associated increase in vascular resistance are thought to be the cause. Guideline-based drug treatment of hypertension is fundamental. When using VEGF inhibitors, regular weekly monitoring during the first cycle of treatment is preferred. Thereafter, monitoring every 2-3 weeks during VEGF inhibitor use is necessary (*68*). Because hypertension has also been reported to be a predictor of treatment response with bevacizumab (*69*) and sunitinib (*70*), proper management of hypertension and avoidance of discontinuation is preferred. Other anti-androgenic and antiestrogenic drugs for prostate cancer can also increase blood pressure.

Arrhythmia

There are a wide variety of arrhythmias that can be caused by anti-tumor treatment (*4,71*). However, data on incidence and causation are scarce. This is because the arrhythmia itself may not be identified if it is transient or asymptomatic. Because of the possibility of fatal arrhythmias, the accumulation of data and the development of high-quality evidence are needed.

QT prolongation

QT prolongation syndrome can result in fatal arrhythmias such as Torsade de pointes (TdP). During chemotherapy, electrolyte abnormalities due to vomiting and diarrhea, especially hypokalemia, may be caused by antiemetic and antipsychotic drugs. It can also be exacerbated by women, the elderly, the presence of underlying cardiac disease, and subclinical congenital long QT syndrome (LQTS) (*4*). Arsenic trioxide, used for treatment of leukemia and myeloma, is a typical agent that causes QT prolongation in 26-93%. In 40% of cases, QT interval is greater than 500 msec and occurs between 1-5 weeks after administration (*72*). Tyrosine kinase

inhibitors also cause QT prolongation. The incidence varies from drug to drug, but is relatively small with vandetanib, lapatinib and others (*4,12*).

ECG and electrolytes are necessary prior to treatment, and ECG is recommended for 7 to 15 days and monthly for the first 3 months after drug administration and change of dose (*4*). When QT prolongation is observed, treatment should be temporarily interrupted and electrolytes should be monitored and corrected, if necessary. Particularly, prolongation of more than 500 msec QTc or more than 60 msec from pre-treatment is associated with a higher risk of transition to TdP. If TdP occurs, tachycardia pacing by temporary pacemaker and/or infusing Mg preparations are required. After improvement in TdP, it is preferable to resume with a smaller dose of chemotherapy if there is no alternative therapy.

Atrial fibrillation

Several reports have revealed a link between cancer and atrial fibrillation (*73*). Atrial fibrillation is common in cancer patients. The development of postoperative atrial fibrillation due to surgical invasion is well documented, especially after lung cancer surgery, with rates as high as 5-28% (*74*). One epidemiological study reported that the incidence of atrial fibrillation was 2.4% at the time of cancer diagnosis, but 1.8% of patients developed new atrial fibrillation after cancer diagnosis (*75*).

Conversely, in a study of women only, 147 of 1,467 (10%) newly diagnosed atrial fibrillation patients were subsequently diagnosed with cancer (*76*). In a comparison of cancer incidence with patients without atrial fibrillation, a significantly higher hazard ratio of 1.48 was reported in patients with atrial fibrillation, even after adjusting for many confounding factors such as age, race, body mass index, hypertension, diabetes, and dyslipidemia. The results were consistent across the different types of atrial fibrillation. The cancer with the highest risk was colorectal cancer, which was reported to have about twice the risk (*76*).

When atrial fibrillation occurs, bleeding complications from thromboembolism and the anticoagulation used to treat it are also problematic, as is heart failure caused by atrial fibrillation. Although there is still no definitive statement on anticoagulation for cancer patients with atrial fibrillation, bleeding risk assessment by HAS-BLED (*77*) and thromboembolic risk by the CHA_2DS_2-VASC might be useful (*74*).

Cancer-associated thrombosis

Although cancer-related deaths are the leading cause of death in cancer patients, thromboembolism is the second most common cause, along with infections (*78*). Cancer-related, particularly venous thromboembolism is called cancer-associated thrombosis (CAT). The risk is also 4.3 times higher in cancer patients than in non-cancer patients (*79*). Causes of thromboembolism in cancer patients include cancer-related factors, patient-related factors, and treatment-related factors (*4*).

Risk Factors

Cancer-related factors include the origin of the cancer. Stomach and pancreatic cancers are at particularly high risk, followed by lung, hematologic, gynecologic, brain, kidney, and bladder cancers. Also, the higher the grade and the more advanced the stage, the higher the risk. It also often occurs within 3 months of cancer diagnosis (*79*). Patient-related factors include hereditary thrombogenic predisposition; comorbidities such as heart, lung, and renal diseases; history of venous thromboembolism; varicose veins in the legs; older age; women; and decreased activity. Treatment-related factors include surgery, radiation therapy, blood transfusion, central venous catheter placement, rest and hospitalization. Hormonal agents such as platinum, anticancer agents, L-asparaginase, and estrogen have long been known to increase the risk of disease (*80*). The occurrence of venous thromboembolism (VTE) has also been reported in more than 10% of myeloma cases (*81*), and the risk is further increased with the use of immunomodulatory drugs (IMiDs) such as lenalidomide, which play a central role in the therapy. VEGF inhibitors such as bevacizumab (*65*) and multi-kinase drugs such as sunitinib are also known to be a risk.

The Khorana score is often used in the identification of high-risk patients with CAT. A score of approximately 2.5 months shows short term thrombosis risk, and a score of 3 or more recommends appropriate VTE prophylaxis (*82*). The COMPASS-CAT RAM has also been used as a predictive score for VTE in patients with breast, colorectal, lung, and ovarian cancer during outpatient chemotherapy (*83*). Anti-hormonal therapy and the use of anthracyclines have been identified as risk factors.

Diagnosis and treatment

Pre-test probability is important in the diagnosis of VTE. Deep venous thrombosis (DVT) is typically accompanied by swelling of the affected lower limb, but is often asymptomatic. Pulmonary thromboembolism (PTE) is a cause of dyspnea and chest pain, but may be detected incidentally on enhanced computed tomography (CT) scan. Wells scores (*84*) are used to assess pre-test probability. D-dimer which is highly sensitive for VTE, can be used to deny VTE if the pretest probability is low and D-dimer is normal (*85*). If the pre-test probability is high, an imaging study should be performed. The first choice for testing for DVT is lower extremity venous ultrasound. Contrast-enhanced CT is necessary because of the ultrasound difficulty in diagnosing abdominal and pelvic areas if a proximal thrombus or PTE is suspected.

Treatment is similar for the treatment of VTE in non-cancer patients; hospitalization and outpatient care are considered depending on the severity of PTE and

DVT. The pulmonary embolism severity index (PESI) score (*86*) and vital signs are evaluated. Treatment is primarily anticoagulant; the ASCO guidelines (*87*) recommend the use of low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), fondaparinux, or rivaroxaban as initial therapy. Vitamin-K antagonists are of limited use when LMWH or direct oral anti-coagulations (DOACs) are not available. The duration of use should be determined taking into account the risk of bleeding and thrombosis. Randomized control trials of DOACs for CAT compared with LMWH were shown noninferior in terms of recurrent thrombosis but more frequent bleeding (*88-90*) (Table 3). For apixaban, there was no significant difference in bleeding between the two groups (*90*). There is no clear evidence for the use of DOACs for prophylaxis; data on primary prevention in patients with high Khorana scores show that the use of DOACs prevents thrombosis but clearly increases bleeding (*91*). It is important to use them with caution in those at very high risk for thrombosis.

Late cardiotoxicity of radiotherapy

Radiation therapy is one of the mainstays of cancer treatment. Irradiation causes damage to DNA strands through the production of reactive oxygen species, which exerts an anti-tumor effect. If the irradiated area includes the heart, various cardiac injuries may occur (*92*).

Coronary artery disease

Radiation-induced coronary artery disease (RI-CAD) is a late complication of radiation therapy, occurring in many cases more than 10 years later (*93*). A recent study found that the incidence of major adverse cardiovascular events increases in proportion to the radiation dose to the heart (*94*). However, there is no threshold, and we know that there is a stochastic effect. It has long been used in Hodgkin's disease and breast cancer, but in recent years it has also been used as preoperative adjuvant or curative chemoradiation in esophageal cancer and non-small cell lung cancer, and in many cases cardiac irradiation is unavoidable. The most common sites of lesions are near the ostium of 3 coronary arteries and the left main trunk. The incidence of RI-CAD has been found to increase with the presence of classical risk factors for atherosclerotic diseases (94). Therefore, intervention according to risk factors and regular checkups are considered necessary. There are still no appropriate recommendations for invasive tests such as coronary CT.

Valvular disease

Radiation has been reported to cause damage to the valve leaflets themselves, resulting in fibrous thickening, shortening, and calcification of the valves and surrounding tissue, leading to valvular heart disease. It is common in aortic and mitral valves. The incidence of valvular heart disease after radiation therapy has been reported variously, but the incidence is less than 10%, and the incidence increases when the radiation dose to the chest exceeds 30 Gy (*4*). Echocardiography is not required routinely before or during radiation therapy, but screening at 10 years and every 5 years thereafter is recommended for high-risk patients, even if they are asymptomatic (*95*).

Pericardial disease

The incidence of acute pericarditis decreases with decreasing radiation dose. Chronic pericarditis or

Table 3. The summary of clinical trials using DOAC for cacer-associated thrombosis

	Rivaroxaban	Apixaban	Edoxaban
Study name	SELECT-D	Caravaggio	Hokusai VTE Cancer
Authors, Year (*Ref.*)	Young AM, *et al.* 2018 (*89*)	Agnelli G, *et al.* 2020 (*90*)	Raskob GE, *et al.* 2018 (*88*)
n	203 *vs.* 203	576 *vs.* 579	522 *vs.* 524
Control	Dalteparin	Dalteparin	Dalteparin
Dose	30 mg bid for the first 3 weeks followed by 20 mg once daily for a total of 6 months	10 mg twice daily for the first 7 days and 5 mg twice daily thereafter	60 mg once daily
Follow-up period	6 months	180 days	360 days
Efficacy outcome	VTE recurrence	VTE recurrence	VTE recurrence
Result, *n* (%)	8 (4) *vs.* 18 (9)	32 (5.6) *vs.* 46 (7.9)	41 (7.9) *vs.* 59 (11.3)
HR [95% CI]	0.43 [0.19 to 0.99]	0.63 [0.37 to 1.07]	0.71 [0.48 to 1.06]
p-value	-	< 0.001 for non-inferiority, 0.09 for superiority	0.09
Safety outcome	Major bleeding and clinically relevant non-major bleeding	Major bleeding according to the criteria of ISTH[†]	Major bleeding according to the criteria of ISTH[†]
Result, *n* (%)	11 (5) *vs.* 6 (3)	22 (3.8) *vs.* 23 (4.0)	36 (6.9) *vs.* 21 (4.0)
HR [95% CI]	1.83 [0.68 to 4.96]	0.82 [0.40 to 1.69]	1.77 [1.03 to 3.04]
p-value	-	0.6	0.04

[†]defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death. CI: Confidence Interval, ISTH: Internationl Society on Thrombosis and Haemostasis, HR: Hazard Ratio, VTE: Venous Thromboembolism,

exudative constrictive pericarditis with effusion may be seen. In rare cases, tamponade may occur, requiring pericardiocentesis. In the case of drug-refractory constrictive pericarditis, pericardiectomy might be required (*4*).

Current Remaining Issues and Future Developments

Onco-cardiology is a field that has just begun to dawn, but is gradually being recognized as a new problem for cancer survivors. Genome analysis is being conducted for chemotherapy-related cardiomyopathy. Mutations in the Titin gene, one of the causative genes of idiopathic dilated cardiomyopathy and other diseases, have been reported to be involved in the development of chemotherapy-related cardiomyopathy (*96,97*). Analysis of such gene mutations or SNPs may allow identification of high-risk groups for chemotherapy-related cardiomyopathy before treatment.

Another issue is the transitional care of the increasing number of childhood cancer survivors. Childhood cancer survivors have a significantly increased incidence of heart failure and other cardiac problems above the age of 35 when compared to their non-cancer survivor siblings and this occurs as a problem in later life (*98*). How to conduct regular follow-up after adulthood has become an issue. There is also an increase in the number of cancers in the younger age group, known as the adolescence and young adult (AYA) generation. When cardiotoxicity occurs at a young age, it is necessary to create a system to provide social, economic, and emotional support in collaboration with various specialties.

Conclusion

The prognosis of cancer has improved by establishment of cancer therapy and development of novel chemotherapy. Now that the patients can live longer, the physician needs to pay attention for cardiotoxicity of cancer therapy and complications of cardiovascular disease. GLS and some biomarkers such as BNP and troponin are useful for early detection of cardiotoxicity, and we have to check them when a high risk drug is used for patients who have high risk background. Dexrazoxane, beta-blockers, ACE inhibitors, and statins are possible treatments to prevent cardiotoxicity. ICI-associated myocarditis is rare but has poor prognosis when it occurs. CMR may be able to detect problems in the early phase and early initiation of high-dose steroids has been reported to improve prognosis. Ischemic heart disease, hypertension and arrhythmia occur due to aging of cancer survivors and using some drugs. CAT can occur, especially in patients with pancreatic and stomach cancer. Randomized control trials of DOACs for CAT compared with LMWH were shown noninferior in terms of recurrent thrombosis but more frequent bleeding except for apixaban. Radiotherapy damage can occur to the coronary artery, as well as valvular and pericardial disease in the late phase.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received March 3, 2021; Revised June 7, 2021; Accepted June 18, 2021.

Released online in J-STAGE as advance publication July 3, 2021.

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