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Diagnosis, Treatment, and Prevention of Cardiovascular Toxicity Related to Anti-Cancer Treatment in Clinical Practice: An Opinion Paper from the Working Group on Cardio-Oncology of the Korean Society of Echocardiography

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Cardiovascular (CV) toxicity associated with anti-cancer treatment is commonly encountered and raises critical problems that often result in serious morbidity or mortality. Most cardiac toxicities are related to the cumulative dose of chemotherapy; however, the type of chemotherapy, concomitant agents, and/or conventional CV risk factors have been frequently implicated in CV toxicity. Approximately half of the patients exhibiting CV toxicity receive an anthracycline-based regimen. Therefore, serologic biomarkers or cardiac imagings are important during anti-cancer treatment for early detection and the decision of appropriate management of cardiotoxicity. However, given the difficulty in determining a causal relationship, a multidisciplinary collaborative approach between cardiologists and oncologists is required. In this review, we summarize the CV toxicity and focus on the role of cardiac imaging in management strategies for cardiotoxicity associated with anti-cancer treatment.

KEY WORDS: Cardiovascular toxicity · Cardio-oncology · Anti-cancer treatment · Echocardiography.

Introduction

Overview of cardiovascular toxicity

Cardiotoxicity associated with chemotherapy frequently raises an important issue in cancer treatment, because it can influence the mortality and morbidity of patients with cancer by causing a delay or discontinuation of chemotherapy.[1)2)] Generally, some requisites are needed to define cardiotoxicity caused by chemotherapy: 1) a cause-and-effect relationship between cardiotoxicity and chemotherapy, 2) a clear mechanism for

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chemotherapy-induced cardiotoxicity, and 3) available indicators or biomarkers for the early detection or evaluation of cardiotoxicity. Considering these findings, physicians should decide whether to continue, discontinue, or delay chemotherapy or whether to reduce the dose of chemotherapeutic agents in case of cardiotoxicity development.[3-6]

For anthracyclines, the mechanism of cardiotoxicity, including left ventricular (LV) dysfunction, has been previously evaluated, and monitoring or detection of cardiotoxicity can be conducted using biomarkers, including troponin-I (Tn-I) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).[7-9] Moreover, to some extent, cardiotoxicity can be prevented with the use of a protectant (e.g., dexrazoxane).[10][11] In contrast, 5-fluorouracil (FU) has an unclear mechanism of cardiovascular (CV) toxicity; cardiotoxicity related to this agent is difficult to detect or monitor and occurs at a variable incidence of 1% to 8%.[12][13] These uncertainties make it difficult to establish consensus on handling cardiotoxicity. Therefore, greater extension of the cardio-oncologic field in cancer treatment is warranted.

Crucial cardiovascular toxicities associated with anti-cancer treatment

A wide spectrum of CV toxicity associated with anti-cancer treatment has been described, and nearly all chemotherapeutic agents can elicit CV toxicity. The prototype of cardiotoxicity is cardiomyopathy or LV dysfunction caused by anthracyclines. Common CV toxicities (Appendix 1 for breast cancer) include 1) cardiomyopathy or heart failure (HF) due to myocardial injury, 2) ischemic heart disease or coronary artery disease, 3) QT prolongation or cardiac arrhythmias, 4) hypertension, 5) thromboembolism, 6) pulmonary artery disease, and 7) pericardial disease.

Cardiomyopathy

Classically, cardiotoxicity associated with anti-cancer treatment has been usually based on the cardiomyopathy with a decreased LV ejection fraction (EF) and HF symptoms (or signs). Cardiotoxicity seems to be limited to a structural disorder, revealed by decreased LVEF, in relation with systolic dysfunction. Therefore, cardiac dysfunction has been defined as a decrease of 10% point from baseline LVEF or an absolute value of LVEF < 53%.[3][4][14][15] However, from a cardiologic perspective, the term "cardiomyopathy" can encompass the preserved LVEF or diastolic dysfunction, when LV strain, rather than LVEF is used to assess cardiomyopathy.[3][15]

Among cardiac toxicities, cardiomyopathy is frequently encountered in the cardio-oncologic field (Table 1). Cardiomyopathy caused by anti-cancer treatment can be classified into type I and type II toxicities.[3][4][15-17] Type I toxicity is characterized by irreversible myocardial damage and is frequently associated with anthracycline use. Type II toxicity is associated with targeted therapy such as trastuzumab, which can cause reversible cardiac dysfunction regardless of chemotherapeutic dose.

Table 1. Common chemotherapeutic agents related with cardiomyopathy

Group	Agent
Anthracyclines	Doxorubicin*
	Epirubicin
	Idarubicin*
Alkylating agents	Cyclophosphamide*
	Ifosfamide*
Antimetabolites	Clofarabine*
Antimicrotuble agents	Docetaxel*
Monoclonal antibody-based tyrosine kinase inhibitors	Bevacizumab*
	Trastuzumab*
Proteasome inhibitors	Bortezomib
Small molecular tyrosine kinase inhibitors	Sunitinib*
	Imatinib mesylate
	Lapatinib
	Dasatinib

*Drugs are considered frequent and important for cardiomyopathy

Anthracyclines

The suggested mechanism of anthracycline-induced cardiotoxicity is oxidative stress with the reactivation of oxygen free radicals or superoxide by iron-anthracycline complex within the mitochondria.[6][8][17] The interaction between anthracycline and topoisomerase II beta results in changes in the transcriptome, mitochondrial dysfunction, and the production of reactive oxygen species.[7] These consequences disrupt the DNA double strand and damage the myocardium. The injured myocardium experiences programmed apoptosis and cell necrosis accelerated by reactive oxygen species.[8][18][19] Other studies have suggested that the anthracycline-mediated mechanism involves the inhibition of adenosine triphosphate in the myocardium and homeostatic changes in calcium metabolism associated with inhibited messenger RNA transcription of Ca-ATPase in the sarcoplasmic reticulum.[2][6] Recently, anthracycline-associated cardiomyopathy has been considered to occur more frequently under conditions of myocardial fibrosis or pressure overload such as hypertension.[19]

Cyclophosphamide/ifosfamide

The suggested CV toxic mechanism of cyclophosphamide, a drug used in lymphoma and breast cancer treatment, has been the extravasation of chemotherapeutic agents with endothelial damage, leading to interstitial edema, hemorrhagic perimyocarditis, and myocardial necrosis with the production of fibrin microthrombi.[2][20-22] Likewise, pericardial effusion can be frequently caused by cyclophosphamide.

Ifosfamide, used for germ-cell testicular cancer treatment, seems to have a similar cardiotoxic pathway, but less frequently causes hemorrhagic myocarditis compared to cyclophosphamide. Other explanations of LV dysfunction can include an indirect pathway, such as an electrolyte imbalance and volume

changes aggravated by direct nephrotoxicity.[23)24)]

Trastuzumab

Trastuzumab, a monoclonal antibody against HER2-ErbB2, has been commonly used in HER2 (+) breast cancer.[25)26)] The cardiotoxic mechanism of this agent is mediated by inhibition of the ErbB2 receptor, which seems to play a major role in the cardiomyocyte proliferation and cardiac development required for cardiac contractility. Cardiotoxicity occurs more frequently when this agent is administered concurrently with anthracyclines.[25)26)]

Bevacizumab

Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor used for metastatic breast cancer or colorectal cancer, can worsen underlying HF, hypertension, and arterial thromboembolism.[27)] The mechanism of CV toxicity of this agent seems to be related to the inhibition of VEGF signaling on vascular smooth muscle cells and the endothelium: CV complications are primarily related with the inhibition of nitric oxide (NO) pathway, activation of endothelin system and vasomotor tone, and promoting changes in the microvasculature.[28-30)] Compared to that observed with trastuzumab, cardiac dysfunction associated with bevacizumab is not common. The risk factors for cardiomyopathy include pre-existing CV disease, concomitant anthracyclines treatment, and old age.[31)]

Ischemic heart disease

Chest pain can be related to ischemic coronary artery disease or non-ischemic disease. Ischemic heart disease is frequently associated with vasoconstriction or vasomotor reactions to chemotherapeutic agents such as 5-FU (Table 2). Vascular toxicities can be classified into type I (irreversible and processed) and type II (reversible and transient) responses. Type I responses are frequently associated with toxic effects on endothelial cells caused by cisplatin, bleomycin, or vinca alkaloids. Type II responses are associated with vasoconstriction or vasomotion induced by 5-FU, capecitabine, paclitaxel, gemcitabine, rituximab, and sorafenib.[32-34)]

Table 2. Common chemotherapeutic agents related with ischemic heart disease

Group	Agent
Antimetabolites	Capecitabine*
	Fluorouracil*
Antimicrotuble agents	Docetaxel
	Paclitaxel
Monoclonal antibody-based tyrosine kinase inhibitors	Bevacizumab*
Small molecular tyrosine kinase inhibitors	Sorafenib*
	Eriotinib

*Drugs are considered frequent and important for cardiomyopathy

Fluorouracil/capecitabine

Up to 20% of cases of vascular toxicity are estimated to be caused by 5-FU.[12)13)35)] The action of this agent is relatively acute or associated with early-onset symptoms, including vasoconstriction. The suggested mechanism involves activation of endothelin-1 from smooth muscle cell hyper-reactivity due to postreceptor alterations of protein kinase-C.[36)]

Paclitaxel

The vascular toxicity of taxanes is mediated by vasospasm which can be induced by overactivated histamine release.[37)] It can cause myocardial ischemia (up to 4%), particularly in patients with underlying coronary artery disease.

Bevacizumab

Bevacizumab, an inhibitor of VEGF signaling, impairs endothelial NO synthase activity, resulting in aggravated or worsening hypertension.[27)] It can induce Takotsubo cardiomyopathy with reduced coronary blood flow.[38)] Moreover, it can prompt platelet aggregation, thrombus formation, and increased blood viscosity.

Arrhythmias

Patients with cancer can experience various arrhythmias, including conduction disorders, tachycardia, or bradycardia.[2)39)] Briefly, cancer enhances the arrhythmogenic milieu; however, arrhythmias may accompany LV systolic dysfunction, ischemia, or hypertension rather than being directly related to chemotherapy-induced cardiotoxicity. Some major chemotherapeutic agents have been related with specific arrhythmias (Table 3). Therefore, decisions regarding anti-arrhythmic drugs or devices usually require a risk-and-benefit evaluation in patients with cancer.[40)]

QT prolongation

QT prolongation is one of the important causes of torsade de pointes, which is associated with sudden cardiac death. The duration of the QT interval is influenced by many risk factors, including female sex, old age (> 65 years), LV hypertrophy, congenital long QT syndrome, hormonal disturbances, electrolyte imbalances, and concomitant drugs use.[2)41)] Several classes of

Table 3. Chemotherapeutic agents associated with cardiac arrhythmias

Arrhythmia	Agent
Sinus bradycardia	Taxane, thalidomide
Atrioventricular block	Taxane, anthracyclines, cyclophosphamide
	5-FU, rituximab
Atrial fibrillation	Alkylating agents, anthracyclines, taxane
	5-FU, gemcitabine
Ventricular tachycardia	Doxorubicin, alkylating agents

5-FU: 5-fluorouracil

Table 4. Chemotherapeutic agents associated with QT prolongation

Group	Agent
Tyrosine kinase inhibitors	Sunitinib, sorafenib, vandetanib, nilotinib
Histone deacetylase inhibitors	Vorinostat, despipeptide (FK-228, romidepsin), panobinostat
Anthracyclines	Doxorubicin
Arsenic trioxide	

chemotherapeutic agents should be used with caution in patients (Table 4); particularly, arsenic trioxide is considered a common drug (with a prevalence of up to 90%).[42] Therefore, to prevent fatal cardiac arrhythmic events, frequent electrocardiographic (ECG) monitoring is recommended and abnormal triggering conditions must be corrected in patients with risk factors.

SUPRAVENTRICULAR ARRHYTHMIA

Regarding supraventricular arrhythmia, premature atrial contraction and atrial fibrillation are common, but their clinical significance is not clear in patients without symptoms. Atrial fibrillation is frequently observed during treatment with alkylating agents (up to 30%), anthracyclines, and antimetabolites.[43] The suggested mechanism of arrhythmia induced by alkylating agents is thought to involve direct irritation of the myocardium.[44]

VENTRICULAR ARRHYTHMIAS

LV dysfunction, ischemia, or QT prolongation are associated with ventricular arrhythmias such as premature ventricular contraction, ventricular tachycardia (VT), or ventricular fibrillation (VF) (torsade de pointes). Despite the lack of arrhythmic data, nonsustained VT can occur during treatment with doxorubicin (5–10%) and taxanes (< 1%).[3] Tyrosine kinase inhibitors and alkylating agents can rarely induce VT.

SINUS NODE DYSFUNCTION AND CONDUCTION DISORDERS

Together with thalidomide, taxanes (paclitaxel) and anti-microtubule agents are usually associated with bradycardia or conduction disorders, such as first degree atrioventricular (AV) block or rarely, asystole.[39][43] The incidence of taxanes-associated bradycardia or AV block has been estimated to be approximately 20%.[45][46] The mechanism seems to involve histamine receptor stimulation and ischemia with reduced coronary perfusion.[47]

HYPERTENSION

Hypertension is frequently encountered in patients with cancer (particularly in renal cancer); apart from old age, it is the most common comorbid condition.[48][49] Anti-cancer treatment-associated hypertension was first described with the anti-angiogenic agent (sunitinib). The VEGF signaling pathway is a critical mediator of tumor angiogenesis. VEGF inhibition contributes to endothelial dysfunction such as inhibition of NO production and enhancing of endothelin system, causing vasomotion and microvascular permeability.[29][30][50] Furthermore, VEGF inhibitor promotes activation of renin-angiotensin-system with renal function deteriorated.[29][30] VEGF inhibitor (bevacizumab, sorafenib, pazopanib, and sunitinib)-associated hypertension is a common side-effect in more than 50% of patients.[51][52] Frequently, sunitinib can increase blood pressure (> 150/100 mm Hg) within the first 4 weeks of therapy.[53]

While anti-angiogenic therapy-associated hypertension was not fully elucidated, diverse underlying mechanisms of this entity have been proposed, including impaired endothelial function secondary to decreased NO availability, increased vascular tone, and decreased microvascular density (rarefaction).[54] In addition to these suggestions, renal dysfunction secondary to thrombotic microangiopathy is considered a specific contributing factor of bevacizumab toxicity.[55] VEGF inhibitor-associated hypertension can occur within a few hours to several months after chemotherapy treatment. Therefore, after the initiation of VEGF inhibitors, frequent blood pressure monitoring is necessary for early detection of hypertension.[56]

THROMBOEMBOLIC DISEASE

VASCULAR TOXICITY

Among vascular toxicities associated with chemotherapy, two components should be addressed. One form of vascular toxicity is acute vasospasm.[57] 5-FU is the most common agent associated with vascular toxicity. Its mechanism is linked with vasoconstriction. Therefore, in patients with underlying atherosclerosis, 5-FU can worsen or aggravate vascular spasm, resulting in acute coronary syndrome, peripheral arterial disease, cerebrovascular disease, or stress-induced cardiomyopathy. The second form of vascular toxicities is arterial thrombosis, which is primarily elicited by reduced NO/prostacyclin signaling and platelet activation. VEGF inhibitors cause endothelial dysfunction and platelet function inhibition, resulting in arterial thrombosis in approximately 4% of patients in addition to venous thrombosis.[58][59] The common drugs associated with arterial thrombosis include tyrosine kinase inhibitors (ponatinib, nilotinib, and dasatinib) and cisplatin.

VENOUS THROMBOSIS AND THROMBOEMBOLISM

Malignancy itself can contribute to hypercoagulability. The incidence of venous thromboembolism is estimated to be approximately 7% in patients with malignancies.[60] Generally, thrombogenic procoagulants production is related to cancer-associated factors and patient-associated factors such as immobility. As a treatment-related factor, vascular toxicity caused by chemotherapy can aggravate hypercoagulability, which may result in activation of the coagulation pathway, induction of the inflammation response, and inhibition of fibrinolytic activity.

Mucin-producing malignancies, such as pancreatic and gastric cancers, metastatic cancers, and other high-risk malignancies (gastrointestinal, bladder, brain, renal, testicular, lung, and lymphoma) are commonly associated with venous thromboembolism.[60][61] A high pre-chemotherapy white-blood cell count (> 11000/L) or platelet count (> 350000/L), anemia (hemoglobin < 11 g/dL), red-blood cell growth factors use, and a high body mass index (> 35 kg/m^2) are considered risk factors for venous thromboembolism.[62] With respect to chemotherapeutic agents, cisplatin, VEGF inhibitors (e.g., bevacizumab), and radiotherapy are associated with venous thromboembolism.[62][63]

Pulmonary hypertension

The relationship between pulmonary hypertension and chemotherapy remains poorly understood and the definite cause-and-effect relationship is unclear. Dasatinib, a tyrosine kinase inhibitor of Bcr-Abl used for leukemia, can cause precapillary pulmonary hypertension. The incidence of dasatinib induced pulmonary hypertension is up to 12%.[64][65] It seems to be associated with VEGF receptor-2 dysfunction or inhibition.[64][66]

Pericardial disease

Pericardial diseases, such as pericardial effusion or acute pericarditis can develop during or after anti-cancer treatment. In cases of pericardial effusion, the cardiac involvement of the underlying malignancy should be considered. Malignancies associated with cardiac involvement are melanoma, leukemia, lymphoma, and lung, breast, and gastrointestinal tumors. However, radiotherapy-induced pericardial effusion is also common during cancer treatment or after two months of treatment or up to 10 years after radiotherapy.[67] Several important chemotherapeutic agents can cause pericardial effusion (Table 5).

Highlights

- Anthracyclines are common drugs that cause myocardial injury and fibrosis which are mediated by the production of reactive oxygen species and the formation of iron-anthracycline complexes.
- Cyclophosphamide is associated with the extravasation of chemotherapeutic agent and endothelial damage, causing hemorrhagic perimyocarditis, myocardial necrosis, and pericardial effusion.

Table 5. Chemotherapeutic agents associated with pericardial effusion

Group	Agent
Anthracycline	Doxorubicin, daunorubicin
Tyrosine kinase inhibitors	Dastanib, imatinib, nilotinib
Antimetabolites	5-FU, cytarabine
Alkylating agents	Cyclophosphamide, ifosfamide, busulphan
All-trans retinoic acid	

5-FU: 5-fluorouracil

- Trastuzumab, an endothelial growth factor receptor targeting agent, inhibits the ErbB2 receptor and prevents the cardiomyocyte proliferation and cardiac development required for cardiac contractility.
- Bevacizumab, a VEGF inhibitor, can aggravate underlying HF, hypertension, and arterial thromboembolism by inhibiting VEGF signaling on vascular smooth muscle cells and the endothelium.
- Type I (irreversible and processed) vascular toxicity is frequently associated with toxic effects on endothelial cells caused by cisplatin, while type II (reversible and transient) toxicity is associated with vasoconstriction, primarily induced by 5-FU.
- Regular and frequent monitoring is required to early detect arrhythmic events or pericardial disease, particularly for anthracycline treatment.

Chemotherapy Associated with Cardiovascular Toxicity

Anthracyclines

General consideration

Anthracyclines are well-known antitumor agents that are used to treat many different cancers, including lymphoma, leukemia, breast cancer, sarcoma, and ovarian cancer. Anthracyclines include doxorubicin, liposomal doxorubicin, epirubicin, daunorubicin, idarubicin, and mitoxantrone. Common side-effects of anthracyclines include nausea, vomiting, alopecia, mucositis, bone marrow suppression, and cardiotoxicity.

Clinical considerations in anthracycline-induced cardiotoxicity

Anthracycline-induced cardiotoxicity is traditionally classified as acute or late onset type. Acute immediate cardiotoxicity after the injection of anthracycline has been reported in < 1% of patients and is characterized by supraventricular arrhythmia, ECG changes, and transient LV dysfunction.[68] Early-onset cardiotoxicity (up to one year after treatment) can occur in 1.6–2.1% of patients, while late-onset cardiotoxicity can occur in 1.6–5% of patients at least one year after treatment.[69-71] Chronic toxicity may occur up to 20 years after the first dose of anti-cancer treatment.[2] Both early- and late-onset chronic cardiotoxicities present as progressive, dilated cardiomyopathy, or HF.[4] A recent continuum paradigm of anthracycline-induced cardiotoxicity has emerged, reflecting the development of subclinical myocardial cell injury, early asymptomatic LVEF reduction, and symptomatic HF if left untreated.[7]

Anthracycline-induced cardiotoxicity is the prototype for type I chemotherapy-induced cardiotoxicity, which is characterized by dose-dependent, irreversible myocardial cell death. The risk for cardiotoxicity increases with cumulative dose of anthracycline (Table 6). A cumulative doxorubicin dose of 400 mg/m^2 determines a 3–5% risk of doxorubicin-induced HF, which

Table 6. Comparison of relative cardiotoxicities according to type of anti-cancer treatment and schedules

Drug	Schedule	Cardiotoxicity index	Recommended max. dose (mg/m^2)
Doxorubicin	Rapid infusion	1	400
Doxorubicin	Weekly	0.7	550
Doxorubicin	24-h infusion	0.62	550
Doxorubicin	48-h infusion	0.57	625
Doxorubicin	96-h infusion	0.5	800–1000
Epirubicin	Rapid infusion	0.44	900
Mitoxantrone	Rapid infusion	2.5	160
Daunorubicin	Rapid infusion	0.5	800
Idarubicin	Rapid infusion	2.67	150
Doxorubicin + dexrazoxane	Rapid infusion	0.5	800–1000
Doxorubicin, 300 mg/m^2 + dexrazoxane	Rapid infusion	0.73	500

increases to 7–26% at 550 mg/m^2 and to 18–48% at 700 mg/m^2.[72] The maximal standard cumulative dose for doxorubicin is 400 to 450 mg/m^2, which is considered to achieve the best anticancer effect at a HF risk of 5%.[9] The relative cardiotoxicities of anthracyclines and infusion schedules are noted in Table 6. The cardiotoxicity index is derived by dividing 400 mg/m^2 as the recommended maximum dose of rapid doxorubicin infusion.

Alkylating agents

Cisplatin

Cisplatin is used to treat osteosarcoma and ovarian, head and neck, esophageal, bladder, and lung cancers.[73] Cisplatin has been reported to cause atrial fibrillation, supraventricular tachycardia, left bundle branch block, myocardial ischemia, and myocardial infarction.[74] It is frequently related to vascular toxicities, hypertension, and cerebral ischemia. Cisplatin is also associated with venous thromboembolism, with an incidence of up to 8% in a retrospective cohort study.[2][75]

Cyclophosphamide

Cyclophosphamide is used to treat lymphoma, leukemia, multiple myeloma, lung cancer, and breast cancer. At low doses, cyclophosphamide is rarely associated with cardiotoxicity. The risk of cardiotoxicity is associated with a high dose of cyclophosphamide (> 150 mg/kg and 1.5 g/m^2/day) and the incidence of HF is 7–28%.[2] The common findings are tachyarrhythmias, low QRS complex voltage, non-specific T or ST segment abnormalities, and AV conduction disturbances.[20][21] In breast cancer, cyclophosphamide is commonly used concurrently and sequentially with anthracyclines, or can be substituted after anthracycline failure.

Ifosfamide

Ifosfamide is a cyclophosphamide analogue that is used to treat soft tissue sarcoma and non-small cell lung cancer. Ifosfamide is associated with arrhythmias, ST segment changes, and HF.[24][74] The incidence of HF is 17% and ifosfamide-induced HF occurs dose-dependently within 6–23 days after the initial dose (more than 12.5 g/m^2).[2]

Antimetabolites

5-fluorouracil

The synthetic pyrimidine metabolite 5-FU is used to treat breast, gastrointestinal, head and neck, and ovarian cancers. Angina-like chest pain is common during 5-FU treatment, particularly with the use of continuous infusion. This type of chest pain is difficult to discriminate from cardiac ischemia or infarction, irrespective of ECG changes. Myocardial ischemia, HF, arrhythmias (including atrial fibrillation, VT, and VF), and cardiogenic shock have rarely been reported.[74] The incidence of myocardial ischemia associated with 5-FU ranged from 1–68%.[2][75] Usually, either chest pain or arrhythmia shows good response to 5-FU discontinuation or calcium channel blockers (CCBs) administration.[75] Although the mechanisms of cardiotoxicity associated with 5-FU are not fully understood, small coronary artery thrombosis, arteritis of small-sized vessels, and vasospasm have been suggested as possible mechanisms.[76]

Capecitabine

Capecitabine is an oral prodrug of 5-FU used to treat metastatic breast and colorectal cancers. The incidence and risk factors of capecitabine-associated cardiotoxicity are not as well defined. ECG changes mimicking ST-segment elevation and normal cardiac markers have been noted in many cases.[2]

HER2-targeted therapy

Trastuzumab, a humanized monoclonal antibody to the extracellular domain of the HER2 receptor, has been widely used as a combination treatment option with paclitaxel for metastatic breast cancer since it was approved in 1988. It has been available as a first-line therapy for HER2 (+) breast cancer since

2005. The estimated incidence of trastuzumab-associated cardiotoxicity is 2–28%: 2–7% with single trastuzumab treatment, 2–13% in combination with paclitaxel, and up to 27% with concomitant treatment with anthracycline/cyclophosphamide.[77-79)]

Unlike anthracycline-induced type I toxicity, the cardiac toxicity caused by trastuzumab is considered type II toxicity, which can resolve almost completely if the drug is discontinued. Despite the limited data for Asian patients, the risk factors for cardiac toxicity include old age (> 50 years), a mildly decreased LVEF, underlying CV diseases, and a previous history of accumulated doses of doxorubicin (> 300 mg/m^2).[80-83)] Recently, regular evaluation of cardiac function every three months has been recommended in trastuzumab treatment.[3)] Furthermore, cardiac Tn-I level and two-dimensional (2D) strain on echocardiography are useful tools for the early detection of LV dysfunction or toxicity and are recommended in every cycle of trastuzumab treatment in high-risk patients.[84-86)]

VEGF INHIBITOR

VEGF, a primary regulator of angiogenesis, is activated through VEGF receptor signaling. It seems likely that VEGF receptor inhibition can prevent tumors with overexpressed VEGF receptors from progression and metastasis. VEGF inhibitors are currently used in combination with many other chemotherapeutic agents for solid tumors, such as metastatic colon and renal cell malignancies. VEGF inhibitors prevent vascular endothelial cells from proliferation, induce their apoptosis, and impair the production of endothelial NO. Therefore, hypertension can occur commonly, and its incidence may be up to 50%. Blood pressure control is frequently poor, particularly in patients with underlying hypertension.[53)87)] Additionally, VEGF inhibitors have been associated with thromboembolism because of disturbances in endothelial function.[88)] According to these vascular toxicity mechanisms, VEGF inhibitors (sunitinib, sorafenib, and pazopanib) can cause myocardial dysfunction within the early treatment period or several months after treatment, although the incidence is not as common as that with anthracyclines or tyrosine kinase inhibitors.[89)90)] In high-risk patients with a previous history of cardiac toxicity, monitoring of cardiac Tn-I or NT-proBNP levels and echocardiography every 2–3 months would be helpful to detect LV dysfunction.

HIGHLIGHTS

- Anthracycline-induced cardiotoxicity can occur during the early or late phase of anti-cancer treatment in proportion to the cumulative dose (> 400 mg/m^2 of doxorubicin).
- Alkylating agents, such as cyclophosphamide and cisplatin can cause vascular toxicity, arrhythmic events, and cardiomyopathy.
- Antimetabolites (5-FU)-associated cardiotoxicity commonly manifests as angina-like chest pain with or without myocardial ischemia.
- Trastuzumab, an HER2-targeted agent, can cause reversible and transient cardiomyopathy, particularly when used concomitantly with anthracycline/cyclophosphamide.
- VEGF inhibitors are frequently associated with vascular toxicities, including hypertension and thromboembolism, through endothelial dysfunction.

PREVENTION OF CARDIOVASCULAR TOXICITY

PREVENTIVE TREATMENT FOR CARDIOVASCULAR TOXICITY

Limited data and studies are available regarding primary prophylactic strategies for chemotherapy. The main goal is to prevent cardiac dysfunction, hemodynamic compromise, and vascular damage, regardless of early- or late-phase treatment. Common cardiac side-effects of anti-cancer treatments include cardiomyopathy caused by type I or II cardiotoxicity, ischemic heart disease, and arrhythmias. Endothelial dysfunction/damage or accelerating atherosclerosis also aggravates vascular toxicity. To prevent these adverse CV events, surveillance-based strategies or serial monitoring can be cost-effective and helpful. In anti-cancer treatments, primary prevention or early detection of LV dysfunction has been a primary focus in breast cancer (Appendix 2).

BETA-BLOCKERS

Beta-blockers (BB), important agents in HF treatment, exhibit an anti-oxidant mechanism in preventing cardiotoxicity. A meta-analysis revealed their efficacy in reducing cardiac toxicity by 70% in most anthracycline-based breast cancer studies.[11)] Carvedilol has been shown to prevent doxorubicin or anthracycline cardiotoxicity.[91)] In the PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy (PRADA) study, however, metoprolol had no effect on LVEF maintenance.[92)] Recently, nebivolol was reported to prevent LV systolic dysfunction in a small study.[93)]

ANGIOTENSIN CONVERTING ENZYME INHIBITORS OR ANGIOTENSIN RECEPTOR BLOCKERS

Enalapril, as a prototype, has been evaluated for the prevention of cardiotoxicity and its early administration was shown to be effective in LVEF recovery.[94)] As combination therapy, enalapril and carvedilol exhibited protective effects against decreased LVEF in a small study.[95)] The relative risk reduction in angiotensin converting enzyme inhibitors /angiotensin receptor blockers (ACEIs/ARBs) was 70–90%.[96)] According to the PRADA study, candesartan showed protective effects in patients with early breast cancer.[92)]

DEXRAZOXANE

Dexrazoxane prevents anthracycline toxicity by reducing toxic radical species and inhibiting anthracycline-iron binding

and subsequent reactive oxygen species due to iron chelation. Furthermore, dexrazoxane can induce the depletion of topoisomerase II beta which can cause to damage DNA through interaction with anthracycline.[10] According to the results of a meta-analysis, dexrazoxane can prevent HF (risk ratio 0.29) without a difference in response rate or survival in patients with advanced breast cancer.[97] However, because of concerns regarding its interference with anti-tumor effects, dexrazoxane use is suggested by the American Society of Clinical Oncology only for metastatic breast cancer treated with a cumulative doxorubicin dose of more than 300 mg/m^2.[98]

STATINS

The pleiotropic mechanism of statins action was found related to their prophylactic effects, such as reducing oxidative stress, cellular inflammation, and cytokine release. To date, however, few consistent data on statin usefulness for prevention or treatment of cardiotoxicity are available. Based on limited studies, statins may be possibly involved LVEF maintenance or reduction in HF risk, including in patients with breast cancer.[99][100] Their relative risk reduction ranged widely from 20–80% compared to placebo.[96] Overall, although clear consensus about the preventive role of statins is currently lacking, they may be emerging promising agents for CV toxicity associated with anti-cancer treatment.

EARLY DETECTION OF CARDIAC DYSFUNCTION

Malignancy is occurring at an increasing rate in elderly patients who frequently have many comorbidities, such as hypertension, diabetes, and stroke. Therefore, screening and early identification of high-risk patients is complex and difficult. It is important to consider risk-stratification for cardiac and vascular complications. The risk of CV complications should be defined and evaluated to optimize anti-cancer treatment without detrimental CV side-effects. Therefore, the goal of cardio-oncologic pretreatment is the comprehensive risk-stratification and prevention of detrimental CV side-effects in proceeding with anti-cancer treatment.

CARDIO-ONCOLOGIC CONSIDERATION FOR CHEMOTHERAPY

In type I cardiotoxicity, the most important factor for preventing cardiac dysfunction is reducing the cumulative dose of anthracyclines. According to the current guidelines, the general risk factors for cardiomyopathy or HF include exposure to multiple cardiotoxic agents, cumulative doses (> 360 mg/m^2 for doxorubicin, > 800 mg/m^2 for daunorubicin, > 120 mg/m^2 for mitoxantrone, > 90 mg/m^2 for idarubicin, and > 720 mg/m^2 for epirubicin), the form of administration (continuous infusion over 6 hours vs. bolus administration), combined treatment modality (radiotherapy or chemotherapy), age (< 15 years or > 65 years), and female sex.[4][40][101-103] A liposome-encapsulated formulation rather than conventional anthracyclines can serve as a strategy to prevent cardiac dysfunction because it could not cross the gap junctions of the cardiac endothelium.[104][105] Regarding the cardiac safety about the combination of trastuzumab with doxorubicin/cyclophophamide/paclitaxel, the potential CV toxicity should be carefully considered in case of adjuvant therapy.[83]

Table 7. Conventional risk factors of chemotherapy induced cardiotoxicity

Female sex
Age (< 18 years old, > 75 years old)
Uncontrolled hypertension or diabetes mellitus
Renal failure
Previous history of cardiotoxicity
Pre-existing heart disease: LV hypertrophy, coronary artery disease
Cardiomyopathy: reduced LV ejection fraction
Concomitant or previous radiation therapy involving heart
Concomitant chemotherapy: anthracyclines/trastuzumab

LV: left ventricular

Other conventional risk factors (Table 7) include hypertension, diabetes, dyslipidemia, myocardial ischemia, arterial thrombosis, and arrhythmias. During or after chemotherapy, uncontrolled hypertension is commonly encountered.

Regarding arrhythmias, anthracycline (doxorubicin), arsenic trioxide, tyrosine kinase inhibitors (sunitinib and vandetanib), and histone deacetylase inhibitors were found associated with QT prolongation, and paclitaxel and thalidomide were found associated with bradycardia.[5] In cases of corrected QT (QTc) prolongation > 450 ms in men (> 460 ms in women), arrhythmic events should be considered. According to National Cancer Institute cancer therapy evaluation program, frequent ECG monitoring is required in cases of grade III or IV QTc prolongation (Grade III; QTc ≥ 501 ms without signs and symptoms, Grade IV; QTc ≥ 501 ms with clinical signs or symptoms).[106] Avoiding drugs that prolong QTc interval and correction of the QTc interval should be considered, or discontinuation of the scheduled chemotherapy regimen may be considered if necessary.[5][40] Therefore, ECG monitoring helps detecting early cardiotoxicity at baseline, at 2–4 weeks, monthly during the first three months, every three months, and then periodically during treatment, depending on the chemotherapy regimen and the patient's status. Patients experiencing diarrhea can be monitored more frequently because of possible electrolyte imbalances, and those receiving arsenic trioxide should be also considered for ECG monitoring.

Overall, the decision to initiate anti-cancer treatment in risk-stratified patients should be made through a multi-team approach. During risk-stratification for breast cancer treatment, patients with high-risk symptoms of HF or asymptomatic LV dysfunction can benefit from a cardio-oncologic consultation.[107]

IMAGING FOR CARDIAC DYSFUNCTION

Whereas chemotherapy frequently causes cardiac toxicity or LV dysfunction, the appropriate time to initiate HF treatment for recovery of LVEF is thought to be within 6 months from chemotherapy to start of HF therapy.[94] To prevent irreversible dysfunction of myocardium, imaging modalities for early detection of LV dysfunction would be required. Regarding imaging studies, echocardiography can be easily used to evaluate LV systolic function, especially using LVEF or strain (Fig. 1). However, to detect early LV dysfunction in an asymptomatic patient, LV strain may be preferred to LVEF. With doxorubicin-based treatment, echocardiography is recommended at baseline (before chemotherapy), every six months within five years after chemotherapy, and when an additional doxorubicin dose of 50 mg/m^2 is administered after a cumulative dose of 240 mg/m^2.[15)108)]

Before trastuzumab treatment, a careful evaluation of biomarkers, conventional risk factors, and echocardiography is necessary. If patients show LV dysfunction before or during chemotherapy, low-dose ACEIs or ARBs, BB, and statins may be useful.[109)] Echocardiographic follow-up is recommended at baseline and every three months during treatment with trastuzumab for LV dysfunction surveillance.[4)15)110)] During chemotherapy, if LVEF declines to 40% (or ≥ 10% point decrease from baseline), chemotherapeutic agents can be reduced or stopped for at least four weeks (or up to eight weeks).[4)111)112)] If LVEF recovers to normal range, or reaches at least 45% with a decrease < 10% point from baseline within four weeks, agents can be resumed.[4)15)110)113)]

Other imaging techniques, including 2D-global longitudinal strain (GLS), three-dimensional (3D)-echocardiography-based LVEF, cardiac magnetic resonance (CMR), or radionuclide planar multi-gated angiography (MUGA), can be used to monitor LV systolic function. However, MUGA has problems in its radiation exposure and cannot evaluate cardiac structure, whereas CMR is not readily accessible. In case of GLS, breast cancer studies, including those on trastuzumab, showed that a relative reduction of 2–15% from baseline GLS was associated with increased rate of cardiotoxicity, and accordingly, reductions > 15% from baseline in GLS have been suggested for detection of LV dysfunction by most experts' consensus statements.[15)86)114-117)]

BIOLOGICAL MARKERS FOR CARDIAC DYSFUNCTION

As a complement to imaging modalities, biomarkers such as Tn-I may be helpful to detect myocardial damage. Cardiac Tn-I level has an excellent negative predictive value (approximately 99%) for cardiotoxicity when measured 1–3 days after each dose and one month after high-dose chemotherapy, and it may be useful even in low-risk patients.[108)] Particularly, elevated Tn-I level during or within three days of chemotherapy has been associated with the occurrence of LV dysfunction.[84)118)] Based on these data, Tn-I level measurement at baseline and periodically, or at each cycle of anti-cancer treatment, seems to be a strong tool for surveillance of myocardial injury, and could be

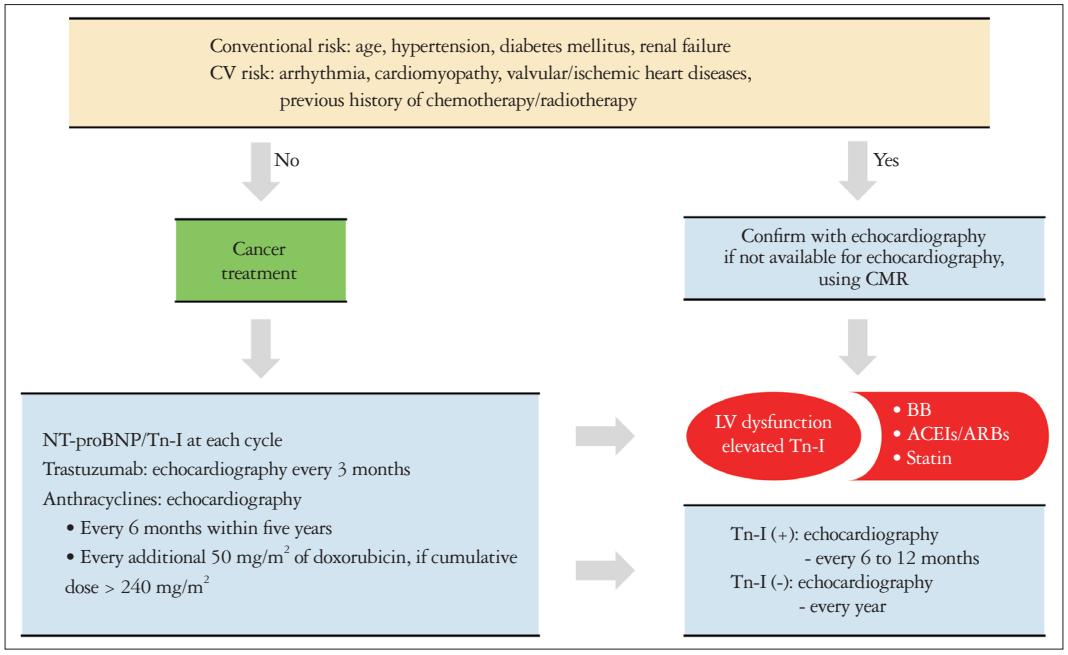

Fig. 1. Flow chart of surveillance and diagnosis of cardiac toxicity in breast cancer treatment. For pretreatment evaluation of breast cancer, conventional and CV risk factors should be assessed. In case of absence of risk factors, anti-cancer treatment could be proceeded. For surveillance of cardiac toxicity, cardiac biomarkers such as NT-proBNP or Tn-I may be useful at each chemotherapeutic cycle, and echocardiography is also required regularly according to the drugs. However, if risk factor is present, echocardiography (or CMR imaging) would be necessary for cardiac function. Overall, LV dysfunction or myocardial injury with elevated Tn-I can be managed with BB, ACEIs/ARBs, or statin. CV: cardiovascular, NT-proBNP: N-terminal pro-B-type natriuretic peptide, Tn-I: troponin-I, LV: left ventricle, CMR: cardiac magnetic resonance, BB: beta-blocker, ACEIs: angiotensin converting enzyme inhibitors, ARBs: angiotensin receptor blockers.

a useful biomarker to screen for subsequent CV events.[4)114)118)]

Contrary to the Tn-I level, the role of the NT-proBNP level in cancer treatment has not been widely evaluated for early detection of LV dysfunction. Generally, the NT-proBNP level is useful for initial risk-stratification and to predict the prognosis of LV dysfunction; persistent elevation of NT-proBNP during a 3-day period of chemotherapy corresponds to a progressive decline in LVEF.[119)]

HIGHLIGHTS

- A baseline CV risk assessment including conventional factors should be performed before anti-cancer treatment.
- For anthracycline-based chemotherapy, serial echocardiography should be performed at baseline, every six months within five years after chemotherapy, and when an additional dose of 50 mg/m^2 is administered (if the cumulative dose > 240 mg/m^2).
- For early detection of trastuzumab-related LV dysfunction, imaging modalities such as echocardiography are recommended at baseline and every three months during treatment.
- As a biomarker, the cardiac Tn-I level is useful for monitoring cardiac tissue injury and can be measured at baseline, within three days, and at each cycle of chemotherapy.
- In cases of LV dysfunction or elevated Tn-I level, BB, ACEIs/ARBs, or statin can be useful to prevent worsening of cardiac function.

DIAGNOSIS OF CARDIOVASCULAR TOXICITY

CARDIAC BIOMARKERS

Cardiac biomarkers have been extensively used to detect cardiotoxicity. Current guidelines suggest Tn-I and NT-proBNP (or BNP) as cardiac biomarkers to detect cardiotoxicity.[3)] Although several studies are ongoing, limited data are available regarding optimal assessment times or frequencies.

TROPONIN I

Out of patients receiving high-dose combination chemotherapy, newly elevated cardiac Tn-I levels can identify those who may have a poor prognosis, when an elevated Tn-I level persists.[120)] Particularly, patients with persistence of Tn-I increase one month after anti-cancer treatment would likely show a great risk of future cardiac event.[118)] Furthermore, in patients treated with trastuzumab with previous exposure to anthracyclines, Tn-I elevation can predict the development of cardiac dysfunction that may not recover despite treatment for HF.[84)] Sawaya et al.[115)] demonstrated that both elevated high-sensitivity (hs) Tn-I levels at three months and a decrease in GLS of echocardiography between baseline and three months were independent predictors of later cardiotoxicity in patients with breast cancer who received anthracyclines and trastuzumab. Ky et al.[85)] also demonstrated that new elevation of serum hsTn-I in patients receiving anthracyclines and/or trastuzumab predicted subsequent LV dysfunction.

N-TERMINAL PRO-B-TYPE NATRIURETIC PEPTIDE

The use of NT-proBNP levels for HF has been widely evaluated and it can be useful to detect high-risk patients, as was reflected in the guideline recommendations.[121)] Recently, a meta-analysis showed that the NT-proBNP level is associated with anthracycline-induced cardiotoxicity and may serve as a useful index for monitoring anthracycline-induced cardiotoxicity at an early stage.[122)]

IMAGING TESTS FOR CARDIOVASCULAR TOXICITY

Anti-cancer treatment is necessary to control a patient's quality of life and to prolong his or her life, but it is also accompanied by increased morbidity and mortality due to CV toxicity.[123)] Cardiac function should be evaluated before, during, and after anti-cancer treatment. Particularly, when the baseline cardiac dysfunction is encountered, the etiology or treatment of LV dysfunction might affect the schedule or protocol of anti-cancer treatment, and thus, the cardio-oncologic evaluation with multi-modalities is frequently required (Fig. 2). Several diagnostic modalities are available to assess LV dysfunction, including ECG, echocardiography, nuclear imaging, CMR, and biomarkers.[124)]

ECHOCARDIOGRAPHY IN CARDIO-ONCOLOGY

2-DIMENSIONAL ECHOCARDIOGRAPHY

LVEF is most commonly used to evaluate LV function. Current guidelines recommend the measurement of LV function at baseline followed by periodic assessments of LV function to detect cardiotoxicity using LVEF calculated by the modified biplane Simpson's method.[15)] Echocardiography is the useful tool for assessing myocardial dysfunction before, during, and after anti-cancer treatment.[15)125)] The currently available echocardiographic criteria for cardiotoxicity are a decrease in LVEF by 10% point or a reduced LVEF < 53%.[3)15)]

TISSUE DOPPLER AND SPECKLE TRACKING ECHOCARDIOGRAPHY

Tissue Doppler imaging and myocardial deformation imaging [strain or strain rate (SR)] might reveal signs of early cardiac dysfunction. Strain, a dimensionless index, reflects the deformation of the ventricular myocardium during the cardiac cycle as a percentage of its initial length, and SR is the rate of deformation or stretch.[86)] The three components of strain and SR are represented in the longitudinal, radial, and circumferential directions.[126)]

The deformation imaging can be provided to evaluate subclinical LV dysfunction caused by anti-cancer treatment.[15)127-129)] Strain and SR have allowed myocardial deformation analysis, and peak systolic SR would be a useful parameter for discrimination of intrinsic contractility.[130)]

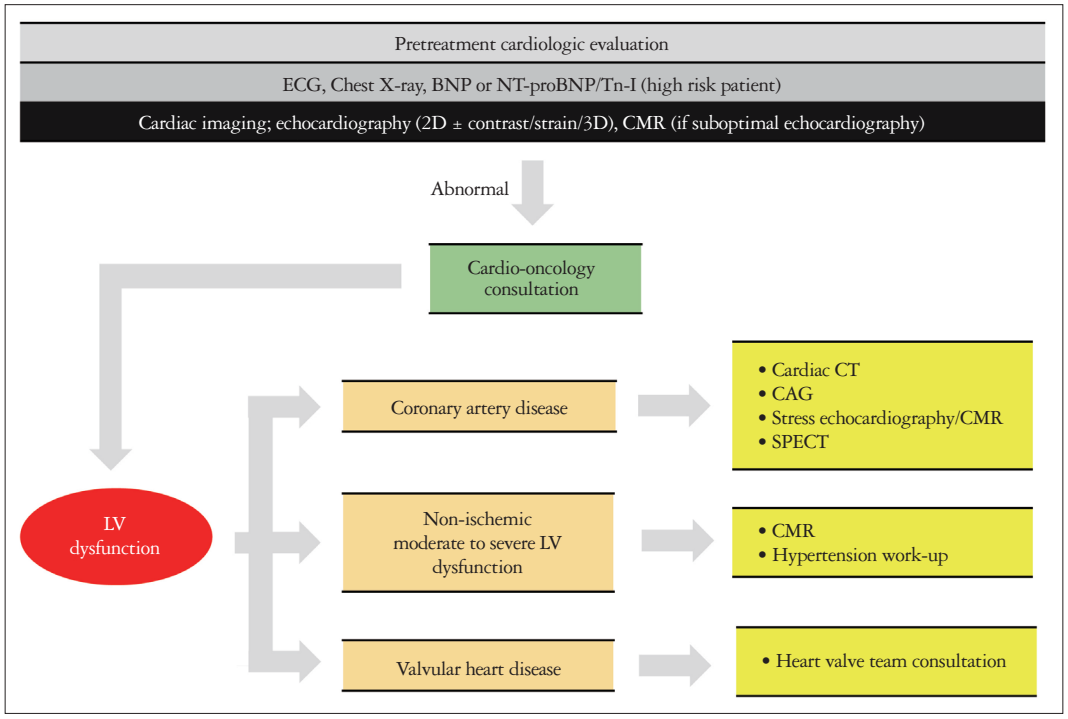

Fig. 2. Approach of LV dysfunction in diagnostic or therapeutic modalities. Baseline cardiac imaging for LV function can be performed using 2D-echocardiography (or contrast-/3D-echocardigraphy) or strain. In case of LV dysfunction, cardio-oncologic consultation is required, and the etiologies of LV dysfunction should be evaluated using appropriate imaging modalities, including CMR, CAG, SPECT, and cardiac CT. ECG: electrocardiography, BNP: B-type natriuretic peptide, NT-proBNP: N-terminal pro-B-type natriuretic peptide, Tn-I: troponin-I, 2D: two-dimensional, 3D: three-dimensional, CMR: cardiac magnetic resonance, LV: left ventricle, CT: computed tomography, CAG: coronary angiography, SPECT: single-photon emission computed tomography.

Recently, GLS has been reported to accurately predict subtle or subclinical LV dysfunction before a decrease in LVEF is evident.[15)130)131)] While the definite, absolute value of GLS based on 2D strain for detecting cardiotoxicity has not been yet clearly elucidated, an optimal cut-off value of 17.5–19% of GLS (Vendor, GE Medical systems) would be useful to detect early cardiotoxicity that needs to be further evaluated.[86)128)] In addition, a reduction in GLS by 15% from baseline is suggested as an indicator of early LV dysfunction, and seems to be more reliable than the absolute GLS value (Fig. 3).[86)127)] However, the same vendor for GLS follow-ups might be necessary with expertise at laboratories whose results show good accuracy and reproducibility.[131)] Even in patients with breast cancer showing normal LVEF, standard anti-cancer treatment could reduce GLS values in addition to other conventional echocardiographic parameters.[129)]

Limitations of Echocardiography

Echocardiography is the standard method for cardiac evaluation of patients with cancer, because it is noninvasive, cost-effective, and widely available. Echocardiography can be performed to detect many complications of cancer therapy, including pulmonary hypertension.[132)133)] It is possible to detect diastolic dysfunction with normal LV systolic function by echocardiography.

Despite the advantages of echocardiography, some limitations should be considered. First, the most important limitation is that echocardiography is operator-dependent; therefore, its reproducibility could be lower compared to that of other imaging modalities. Second, image quality can be poor in some patients. Third, for GLS measurements, there are inter-vendor variabilities and some technical requirements are necessary. To improve reproducibility, the use of 3D echocardiography may be helpful; this technique is associated with the best test-retest variability.[134)]

Cardiac Magnetic Resonance in Cardio-Oncology

CMR is a useful imaging methodology because of excellent spatial resolution and the lack of exposure to ionizing radiation. The most attractive advantage is its ability to detect early or subclinical CV injury before overt manifestations of clinical side-effects of chemotherapeutic agents emerge.[135)] Despite the increasing application of CMR in cardio-oncology, the risk of side-effects such as nephrogenic systemic fibrosis in patients with renal dysfunction (e.g., estimated glomerular filtration rate < 30–40 mL/min/1.73 m^2) or other contraindications to CMR should be always considered.[136)]

Cardiac Tissue Characterization

Tissue injury caused by chemotherapy leads to early (acute or subacute) toxicity, including inflammation and edema, and late

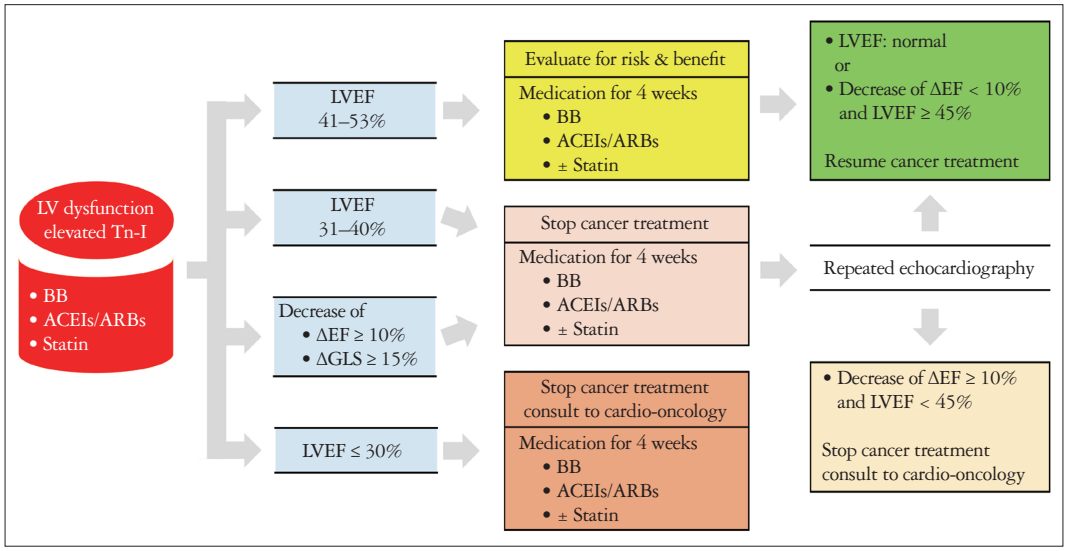

Fig. 3. Flow chart of approach for cardiac dysfunction during breast cancer treatment. Treatment with BB, ACEIs/ARBs, or statin is required for LV dysfunction. According to the strain and LVEF using echocardiography, the risk-and-benefit for breast cancer treatment should be evaluated. If necessary, cancer treatment could be stopped for 4 weeks and re-evaluation of LV function is required using repeated echocardiography. Tn-I: troponin-I, BB: beta-blocker, ACEIs: angiotensin converting enzyme inhibitor, ARBs: angiotensin receptor blockers, LV: left ventricle, EF: ejection fraction, GLS: global longitudinal strain.

(chronic) toxicity, including fibrosis or scar formation. These cellular features can be identified by CMR with T2-weighted images, late gadolinium enhancement (LGE) images, or mapping techniques.[137-139] T2-weighted imaging or T2-short tau inversion recovery (STIR) can reveal inflammation and cellular edema among early histopathological changes. In early hyperemia caused by chemotherapy, increased blood volume or capillary leakage can lead to an increased uptake of gadolinium which shortens T1 time in the phase of myocardial early enhancement.[137] In T2-weighted imaging or T2-STIR, water content causes high signal intensity in injured myocardium.[140] Moreover, within three months after chemotherapy, contrast-enhanced T1-weighted imaging can reveal early signs of subclinical injury or reduced LVEF.[140][141]

After chronic exposure to chemotherapy, chronic, irreversible pathologic changes such as interstitial fibrosis or cellular death appear bright with high signal intensity on LGE images. With recently developed mapping techniques using T2 or T1-LGE, T2-mapping can measure the water content in edematous regions. For extracellular volume (ECV) mapping, T1 mapping before and after enhancement (shortened T1 value) can be used to quantify ECV parameters, which show good correlations with the severity of diffuse fibrosis.[142][143] However, limited evidence that these early myocardial changes contribute to late sequelae or the prognosis of CV events is currently available.

CARDIAC FUNCTION

With respect to LV dysfunction, LVEF is the most important parameter for the diagnosis and evaluation of HF. CMR using a cine steady-state free precession sequence has been regarded as the gold standard for evaluating LVEF, including LV volume, right ventricular volume, and LV mass.[135] With early subtle changes beginning just after the initiation of chemotherapy, LV mass could increase within several days of treatment due to myocardial edema.[144]

During early cardiac toxicity, it is uncertain whether the changes in LV strain can be observed. However, after 1–3 months of chemotherapy, a significant decrease in LVEF and an increase in the LV end-systolic dimension may reflect early cardiac injury. With these findings, subtle diffuse LV fibrosis can be detected via LGE-T1 signal intensity without focal regional enhancement or myocardial edema.[139-141]

Relative to late cardiac toxicity, approximately a quarter of patients treated with chemotherapy show a decrease in LVEF to less than 50–55%, which is usually accompanied by increased LV end-systolic dimensions. Decreased LV mass is also a crucial marker of late toxicity and seems to be an independent predictor of adverse CV outcomes.[144] The features of fibrosis indicated by LGE T1 imaging are frequently associated with irreversible LV dysfunction and poor prognosis.[135][139][142]

VASCULAR INJURY

In addition to cardiac toxicity, chemotherapy can accelerate or contribute to the development of vascular events, such as hypertension, peripheral arterial disease, or cerebrovascular disease. Unlike atherosclerotic changes, arterial stiffening can be observed via 4D-flow pulse-wave velocity early after the administration of chemotherapy using the phase contrast CMR technique.[135][145][146] Vascular injuries are associated with endothelial or vasa-vasorum dysfunction according to pulse-wave velocity or flow-mediated dilation.[147] Vascular wall thickness and plaque composition can be also assessed by CMR.

Radionuclide imaging in cardio-oncology

Although radionuclide imaging has been used to evaluate cardiac function before and after anti-cancer treatment, its use in clinical practice is decreasing due to limited availability, low spatial resolution, and radiation exposure.[148] Furthermore, it cannot provide information about cardiac structure or LV diastolic function. 2D-echocardiography has been the most widely used modality to assess cardiac function because of its feasibility and accessibility. 2D or 3D echocardiography-based LV volume or LVEF could be an excellent replacement of planar MUGA. Despite the disadvantages of radionuclide imaging, myocardial biological studies on the reversibility or early detection of cellular injury may provide a promising modality to evaluate cardiac toxicity in anti-cancer treatment.[149] Therefore, novel nuclear imaging techniques are currently under investigation for the detection of early LV dysfunction.

Cardiac function

Multi-gated radioactivity counts over several cardiac cycles are performed to assess LVEF using ^{99m}Tc-erythrocytes from the cardiac blood pool. The change in radioactivity between diastole and systole reflects the LV volume change, although soft tissue attenuation is a troublesome limitation.[148] Because of the advantages of accuracy and the lack of an association with geometrical assumptions of LV, MUGA has been frequently used for serial measurements of LVEF.[150] In doxorubicin chemotherapy, a decline in LVEF > 15–20% point from baseline or an LVEF < 30% indicates cardiac toxicity, warranting frequent monitoring and possible treatment-discontinuation.[151]

Furthermore, ^{99m}Tc-gated blood pool single photon emission computed tomography (SPECT) can be used to evaluate LV wall motion and LV volume changes. Recently, 3D-MUGA was proposed as a suitable method for assessing LV volume or dys-synchrony.[152][153]

Cardiac cellular injury

Nuclear imaging has been developed for functional cellular study. Among the techniques using radiotracers, iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) and ^{111}In-antimyosin are frequently used in clinical practice.[154-157] In cardiac sympathetic imaging, ^{123}I-MIBG uptake is related to the efferent sympathetic nervous innervation around the heart. Therefore, using planar scintigraphy, both early and late ratios of heart to mediastinal (H/M) uptake can be calculated.[155][156] ^{123}I-MIBG shows dose-dependent decreased uptake after chemotherapy, reflecting LV dysfunction in late cardiac toxicity. Patients with an H/M ratio < 1.6 showed adverse cardiac events.[158] Therefore, ^{123}I-MIBG can serve as a monitoring tool for the risk of developing cardiomyopathy due to cardiac sympathetic damage.

^{111}In-antimyosin can bind to intracellular myosin which is released from disrupted cardiac sarcolemma, when myocardial necrosis or irreversible cellular damage occurs in myocarditis or myocardial infarction. Regarding myocardial cell injury, ^{111}In-antimyosin uptake during or after anti-cancer treatment could be helpful in risk-stratification for cardiac prognosis or in identifying subclinical LV systolic dysfunction.[156][157] ^{123}I-methylpentadecanoic acid, a radiotracer of free fatty acids, can be used for the early detection of myocardial dysfunction due to decreased mitochondrial uptake of free fatty acids in taxanes-based chemotherapy.[159][160] In particular, ^{111}In-trastuzumab SPECT has been under investigation to determine the direct effect of trastuzumab on the HER2 receptor.[161-163]

Positron emission tomography

Cardiac positron emission tomography has been used to detect highly metabolic tissues, such as malignancy or inflammation, using two radionuclides relative to cardiac metabolism and perfusion. However, its role in detecting early LV dysfunction is still limited due to its high cost and low availability.

Highlights

- To early detect LV dysfunction, echocardiography and cardiac biomarkers are preferentially recommended.
- In cases of suboptimal or imprecise findings on echocardiography, CMR can be used.
- CMR can provide an excellent imaging modality to evaluate myocardial tissue injury, such as inflammation or edema.
- Regarding LV dysfunction, LGE by CMR can provide prognostic information for adverse CV outcomes.
- The measurement of LVEF can be assessed by MUGA when 2D/3D echocardiography or CMR is unavailable.
- Subclinical biological evaluations of cardiomyocytes using SPECT or radionuclide imaging with ^{111}In-antimyosin, ^{123}I-MIBG, or ^{111}In-trastuzumab may serve as a promising strategy to detect cardiac toxicity.

Management of Cardiovascular Toxicity

Heart failure

Although patients receiving potentially toxic chemotherapy were excluded from large randomized HF trials, the management of chemotherapy-related LV dysfunction is considered the same as that for any form of LV dysfunction.[164][165] In the American College of Cardiology Foundation/the American Heart Association guidelines, patients with cancer treated with potentially cardiotoxic agents are classified as patients at a high risk for HF development (stage A).[164] In patients in stage A, the risk factors for coronary artery disease should be controlled, and ACEIs or ARBs should be considered for the treatment of hypertension.[164] For patients with asymptomatic LV dysfunction (stage B), limited data showed some benefits of slowing or reversing LV dilation; despite the lack of evidence, treatment with ACEIs (or ARBs) and a BB should be considered for patients with asymptomatic LV dysfunction or a decline in LVEF < 10% point of the lower normal limit.[3] For patients with symptomatic LV dysfunction (stage C and D),

Table 8. Summary for management of cardiovascular toxicity

Toxicity	Management
Heart failure	Avoid risk factors
	Diuretics, BB, MRA, ACEIs or ARBs
	CRT or ICD
Ischemic heart disease	Nitrate or nitroglycerine
	Antiplatelet agent, anticoagulation
	BB, CCB, ACEIs or ARBs
	Lipid-lowering agents
	Coronary revascularization (intervention or surgery)
Hypertension	Diuretics, DHP-CCB, BB, ACEIs or ARBs
Arrhythmia	
QT prolongation	Avoid risk factors, ICD in cases of VT or VF
Atrial fibrillation	Rhythm control: cardioversion
	Rate control: BB, digoxin, non-DHP-CCB
Acute pericarditis	Aspirin, NSAID, colchicine
Pericardial effusion	Pericardiocentesis, pericardiotomy
Pulmonary arterial hypertension	Ambrisentan, iloprost
Venous thromboembolism	Anticoagulation

BB: beta blocker, MRA: mineralocorticoid receptor antagonist, ACEIs: angiotensin converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CRT: cardiac resynchronization therapy, ICD: implantable cardioverter defibrillator, CCB: calcium channel blocker, DHP: dihydropyridine, VT: ventricular tachycardia, VF: ventricular fibrillation, NSAID: nonsteroidal anti-inflammatory drug

ACEIs (or ARBs if there is a contraindication or intolerance) and BB are recommended, and mineralocorticoid receptor antagonists can be given if symptoms persist (Table 8). Recent trials and updated guidelines recommend an angiotensin receptor-neprilysin inhibitor (ARNI) (sacubitril/valsartan) rather than ACEIs (or ARBs) if symptoms persist, and ivabradine may be recommended in symptomatic patients with sinus rhythm and a heart rate above 70 bpm.[166] However, the data on ARNI and ivabradine are currently limited.

Another important point about the recovery of cardiac dysfunction is the timing of treatment initiation with ACEIs and BB. In patients with type I cardiotoxicity, early treatment with ACEIs (enalapril 2.5–20 mg/day) and/or BB (carvedilol 12.5–50 mg/day) immediately after cardiac dysfunction is detected may result in better cardiac outcomes.[94][167] However, the role of HF medications in the management of type II cardiotoxicity with trastuzumab remains uncertain. Initial studies on trastuzumab-induced cardiomyopathy revealed that cardiac function could be restored by withholding trastuzumab (for a mean of 1.5 months).[168] However, trastuzumab is a crucial treatment for breast cancer and a "drug holiday (cessation)" may be detrimental.[169-171] Whether continuation of trastuzumab with cardioactive protective medication improves outcomes also remains uncertain.

Another issue is the lack of rationale for the management of patients with recovered LV function. It seems reasonable to maintain treatment during periods in which a patient needs more chemotherapy. After cure is achieved, some experts recommend maintaining treatment for at least one year, although others suggest that treatment should be extended in the absence of contraindications.[172]

MYOCARDIAL ISCHEMIA AND CORONARY ARTERY DISEASE

The administration of cytotoxic agents in anti-cancer treatment increases the risk of myocardial ischemia through various mechanisms (coronary vasospasm, thrombosis, and vascular dysfunction). In anti-cancer agent-induced coronary spasm, it is important to identify the temporal relationship between drug administration and the occurrence of chest pain. If symptoms occur during drug administration, the drug should be stopped and then symptoms can be treated with sublingual nitroglycerin and opioids.[112] Although prophylactic therapy with nitrates and CCBs does not appear to be universally effective, these are the only available options.[173]

In radiation-associated ischemia, patients with stable angina can be managed in the same manner as patients with stable angina due to atherosclerotic coronary artery disease and those with unstable symptoms can be managed according to the existing acute coronary syndrome guidelines.[174][175]

Invasive treatment can be considered based on the severity of coronary artery disease, the stage of malignancy, the condition of patient, thrombocytopenia, and the need for future cancer surgery. For revascularization of coronary stenosis, cancer surgery planned in the near future and occurrence of severe thrombocytopenia should be addressed in case of percutaneous coronary intervention (PCI) using dual antiplatelet therapy (DAPT). In other cases, coronary artery bypass graft (CABG) surgery could be an alternative. However, the disadvantage of CABG surgery, including an impaired wound healing, postoperative infection, or prolonged recovery time should be also considered. Therefore, therapeutic options may be individualized according to the risk of the revascularization methods, the urgency of coronary artery disease, the risk of the surgery, and the likelihood of severe coronary artery disease.[176][177] According to the Society for Cardiovascular Angiography and Interventions Consensus, when selecting a stent, bare-metal stents or new-generation drug-eluting stents are recommended because of their low risk of thrombosis.[178] To reduce the need for DAPT, drug-eluting balloons, or bio-absorbable polymers/scaffolds may be used. In all patients receiving PCI, an activated clotting time > 250 seconds is necessary during the procedure. For patients with cancer and severe thrombocytopenia (< 50000/mL), lower doses of unfractionated (30–50 U/kg)

heparin can achieve a therapeutic activated clotting time.[178] Antiplatelet treatment should be individualized. The platelet count > 10000/mL usually allows treatment of aspirin, and DAPT may require a platelet count > 30000–50000/mL.[178]

Arrhythmias

QT prolongation

Although anti-cancer drug-induced QT prolongation may lead to substantial risks of life-threatening cardiac arrhythmias such as torsade de pointes, the potential benefit of chemotherapy over the risk of QTc prolongation may be considered in patients with cancer.[179-181] Discontinuation of anti-cancer drugs is required in case of significant QTc prolongation, serious arrhythmias (torsade de pointes), symptomatic HF, shock, or syncope. Above all things, however, it is important that arrhythmic triggering conditions are corrected.

Atrial fibrillation

It may be reasonable to consider recovery and maintenance of sinus rhythm using cardioversion and/or antiarrhythmic therapy if symptoms persist despite appropriate heart rate control with BB or non-dihydropyridine (DHP) CCBs.[182] The clinical situation dictates the decision to continue the use of the presumed offending anticancer agent. However, the presence of atrial fibrillation alone could not provide a sufficient reason for the cessation of anti-cancer treatment.

The use of warfarin or novel oral anticoagulants (NOAC) in the setting of chemotherapy is another issue. Generally, the risk of thromboembolism and bleeding in patients with atrial fibrillation can be generally assessed by CHA_2DS_2-VASc and HAS-BLED scores despite the lack of validation in patients with cancer.[183] In patients with CHA_2DS_2-VASc scores ≥ 2, anticoagulation can be considered if the platelet count is > 50000/mL.[184] Even in low-risk patients, given the risk of venous thromboembolism, prophylaxis may be considered.

Anticoagulation options include low-molecular weight heparin, vitamin K antagonist, or NOAC. Warfarin is often avoided in patients with metastatic cancer or a high bleeding risk. In patients requiring multiple procedures, patients with a high potential for drug-drug interactions, or patients with a high risk for bleeding, alternative drugs such as low-molecular weight heparin may be suitable for anticoagulation.[185] Although there is a lack of consensus, some clinical studies for active cancer patients with atrial fibrillation showed the comparable safety and efficacy of NOAC for stroke prevention.[186][187]

Hypertension

Treatment for anti-cancer drug-induced hypertension can be initiated with diuretics, BB, ACEIs, ARBs, or CCBs. The choice of anti-hypertensive drug should be tailored to the clinical situation, including consideration of possible drug-drug interactions, volume status, and renal function.[188] ACEIs or ARBs are usually recommended for patients with metabolic syndrome, proteinuria, or a high risk for chronic kidney disease. While DHP CCBs are useful for old age, non-DHP CCBs are not recommended for patients receiving cytochrome-P450 inhibitors.[98][189] Weekly blood pressure monitoring is recommended during the first cycle of therapy and then every 2–3 weeks during anticancer therapy.[112]

Thromboembolism

Malignancy is frequently associated with a prothrombotic or accelerated coagulation cascade. A patient's life expectancy and bleeding risk should be always assessed when deciding whether to administer anticoagulants. Thromboembolic events can be aggravated by several drugs, such as cisplatin, thalidomide, lenalidomide, or vorinostat. Therefore, thromboprophylaxis with low-molecular weight heparin or low-dose aspirin is recommended in acute hospitalized patients with active malignancy, patients undergoing major cancer surgery, and patients with ambulatory multiple myeloma receiving chemotherapy.[190] In ambulatory patients receiving chemotherapy, the role of prophylactic antithrombotic agents remains controversial and the bleeding tendency with anticoagulation drugs should be considered in cases of primary prevention even though venous thromboembolism is common.[191]

In acute venous thromboembolism, a 3 to 6-month regimen of low-molecular weight heparin is recommended in hemodynamically stable patients.[3] Low-molecular weight heparin would be superior to warfarin in reducing recurrent thromboembolic events with comparable mortality and bleeding risk in patients with cancer.[192] The clinical evidence of NOAC efficacy in patients with cancer is limited. In clinical trials, NOAC and warfarin showed no difference in recurrent thromboembolism and bleeding events.[193][194] However, few direct comparative studies between NOAC and low-molecular weight heparin are available.

In order to decide whether anticoagulation should be continued, careful discussion with a detailed overview of cancer therapy, thromboembolic risk, bleeding risk, and patient preference is necessary.[3] In cases of recurrent venous thromboembolism despite anticoagulation treatment, switching from warfarin to low-molecular weight heparin or increasing the dose of low-molecular weight heparin may be considered.[195] Long-term anticoagulation may be required to prevent recurrent thromboembolic events after acute-phase treatment until a cure is achieved because patients with cancer have a high risk of recurrent thromboembolic events. An inferior vena cava filter may be implanted if anticoagulation therapy is contraindicated or fails.[195] However, the risk of filter-related complications, such as filter thrombosis and occlusion should also be considered before implantation.

Because of the increased risk of bleeding, the benefits of thrombolytic therapy in patients with hemodynamically unstable pulmonary thromboembolism remain controversial.[3]

Thrombolytic therapy is absolutely contraindicated for malignant brain tumors.[196] Surgical thrombectomy may be considered, but surgical treatment may carry a high bleeding risk and significant morbidity.[194] Venous thromboembolism may be detected incidentally during imaging for cancer. Since recurrent thromboembolic events and mortality are increased in these patients, incidentally detected asymptomatic venous thromboembolic disease can be treated as a symptomatic event.[197]

PULMONARY HYPERTENSION

Baseline assessment, including CV risk factors, functional capacity (e.g., NYHA/WHO functional class and 6-minute walking distance), cardiac biomarkers (NT-proBNP), and echocardiography is recommended in all patients receiving chemotherapeutic agents known to cause pulmonary hypertension.[3] In patients complaining of dyspnea or exercise limitations during cancer therapy, an echocardiographic examination may be considered.[3] Further cardiologic examinations such as right heart catheterization may be needed in patients with echocardiographic evidence of pulmonary hypertension and right ventricular overload to confirm pulmonary hypertension and to determine the etiology.[198] Assessment of functional capacity and echocardiographic surveillance may be considered every 3–6 months in the setting of treatment with drugs associated with pulmonary hypertension, even in asymptomatic patients.

If drug-induced pulmonary arterial hypertension is detected, referral to a specialized pulmonary hypertension center and a multidisciplinary team approach are recommended to determine whether or not to continue anti-cancer treatment even using pulmonary arterial hypertension-specific drugs.[198] Particularly, dasatinib, a tyrosine kinase inhibitor, frequently induces severe precapillary pulmonary hypertension, but this is often reversible after drug discontinuation.[65] In cases of pulmonary arterial hypertension associated with drugs and toxins (WHO group I), ambrisentan or iloprost inhaler can be used as target therapy. Cyclophosphamide and other alkylating agents may cause pulmonary veno-occlusive disease which has no effective pharmacologic treatment.[199]

PERICARDIAL DISEASE

Several chemotherapeutic agents and chest radiotherapy can cause various pericardial diseases, including acute pericarditis, pericardial effusion, and constrictive pericarditis. Each specific management strategy follows general treatment principles.[200] Aspirin or non-steroidal anti-inflammatory drugs are the mainstays of therapy for acute pericarditis and colchicine is recommended to reduce inflammation and to prevent recurrence.[201] Pericardiocentesis should be considered in patients with hemodynamically unstable pericardial effusion, and it may be considered to relieve symptoms and establish a diagnosis in patients with extensive pericardial effusion.[202] Pericardiotomy can be considered if pericardiocentesis cannot be performed.[203] Surgical pericardiectomy is rarely indicated for constrictive pericarditis or for the management of procedure-related complications.

MECHANICAL CIRCULATORY SUPPORT IN PATIENTS WITH CANCER

Quality-adjusted life expectancy and underlying cancer status are always considered before the implantation of mechanical circulatory devices. Mechanical circulatory support as a bridge to transplantation or destination therapy is not recommended in patients with an active hematologic or solid organ malignancy and a life expectancy < 2-year. However, patients who have been treated for cancer and have maintained disease-free status may be candidates for mechanical circulatory support as a bridge to transplantation. Mechanical circulatory support as destination therapy may also be considered in patients with a life expectancy > 2-year.[204]

HIGHLIGHTS

- The conventional treatment of HF requires the use of BB, ACEIs (or ARBs), or aldosterone blockers according to guidelines, but the data are limited.
- In cases of symptomatic ischemic disease, anti-cancer treatment should be stopped, and evaluation with treatment is recommended.
- Significant symptomatic QT prolongation should be addressed through the correction of triggering factors; discontinuation of anti-cancer treatment may be considered.
- Prophylactic anticoagulation for venous thromboembolism is recommended after cancer surgery for a minimum four weeks. Long-term anticoagulation may be considered to prevent recurrent thromboembolic events after the acute phase of treatment until the cancer is cured.

FUTURE DIRECTIONS

The CV side-effects or toxicities caused by anti-cancer treatment have a critical impact on the evaluation and future treatment of malignancies. Unfortunately, few studies regarding the cause-and-effect relationship between cardiotoxicity, treatment, monitoring, and biomarkers in the prevention of LV dysfunction are currently available. To increase treatment effectiveness for cardiotoxicity, primary prevention using precise, easy, and simple methods to detect side-effects is necessary. Advances in imaging modalities and the availability of cardiac biomarkers can contribute to early diagnosis, leading to better quality of life in patients with cancer. Together with these developments, a prediction model for CV toxicity is needed for risk-stratification relative to CV prognosis. Future studies in the cardio-oncologic field should gather data regarding the mechanism and prevention of the cardiotoxicity associated with anti-cancer treatment. Therefore, close collaboration between cardiology and oncology teams is necessary.

Reviewers

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□ Appendix for Breast Cancer Cardio-Oncology □

Appendix 1. Adverse cardiovascular side-effects

1. Cardiomyopathy
   1) The most common cause of drugs
      (1) Anthracycline: Doxorubicin (a cumulative dose of > 400 mg/m^2)
      Epirubicin (a cumulative dose of > 900 mg/m^2)
      (2) Trastuzumab
      (3) Small molecule tyrosine kinase inhibitors: sorafenib, sunitinib, pazopanib
      (4) 5-fluorouracil
      (5) Cyclophosphamide (in combination with anthracycline)
      (6) Docetaxel
   2) Time onset: few months to years after treatment
2. Ischemic heart disease
   5-fluorouracil, capecitabine (Xeloda), taxanes, bevacizumab (Avastin), cisplatin
3. Venous thromboembolism/stroke
   Cisplatin, selective estrogen receptor modulator (SERM): tamoxifen
4. Hypertension
   1) Small molecule tyrosine kinase inhibitors: sorafenib, sunitinib, pazopanib
   2) Vascular endothelial growth factor inhibitors: bevacizumab
5. QT prolongation
   Doxorubicin, SERM (tamoxifen)

Appendix 2. Prevention and treatment of cardiovascular side-effects

1. Beta-blocker, angiotensin-converting enzyme inhibitor/-receptor blocker, statin
   1) For asymptomatic or symptomatic structural heart disease
   2) For elevated cardiac Tn-I or NT-proBNP
2. Dexrazoxane
   For metastatic breast cancer (> 300 mg/m^2 of doxorubicin)
3. Monitoring of cardiac function and cardiac biomarkers
   1) Echocardiography, cardiac MR
   2) Tn-I, NT-proBNP