Review

Optimal management of coronary artery disease in cancer patients

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Abstract

Owing to early diagnosis and rapid development of treatments for cancers, the five-year survival rate of all cancer types has markedly improved worldwide. Over time, however, there has been an increase in the number of cancer patients who develop coronary artery disease (CAD) due to different causes. First, many risk factors are shared between cancer and CAD. Second, inflammation and oxidative stress are common underlying pathogeneses in both disorders. Lastly, cancer therapy can result in endothelial injury, coronary artery spasm, and coagulation, thereby increasing the risk of CAD. As more cancer patients are being diagnosed with CAD, specialized cardiac care should be established to minimize the cardiovascular mortality of cancer survivors.

Owing to the unparalleled growth in cancer therapy over the past decades, the average five-year survival rate of cancer patients has reached 67% in developed countries.[1] However, the number of cancer patients with coronary artery disease (CAD) continues to increase because of the cardiac toxicity exhibited by anticancer drugs and the common pathogenesis between cancer and CAD. Presently, there are no guidelines for cancer patients with CAD. Therefore, multidisciplinary collaboration is needed to formulate reasonable strategies for the diagnosis and treatment of CAD in cancer patients.

Epidemiology of cancer-related CAD

Over the last 40 years, the 10-year survival rate of early breast cancer has increased from 40% to 80%, and a similar growth has been found in other cancers, such as solid cancers and hematologic cancers.[2–4] Unfortunately, improvements in cancer prognosis have been achieved at the cost of cardiovascular toxicity. Thus, cancer survivors have an increased

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medium-to long-term risk of CAD development.[5] In newly diagnosed cancer patients, the 6-month cumulative incidence of myocardial infarction was found to be markedly higher than that of matched control patients ($HR = 2.9$).[6] A similar issue could also be present in childhood cancer survivors. A prospective study of 7289 childhood cancer survivors revealed that the cumulative incidence of CAD was approximately 10% at 10 years from cancer diagnosis.[7] There has also been an increase in the incidence of cancer in patients with acute coronary syndrome (ACS). A prospective study with 17 years of follow-up demonstrated that the incidence of malignant tumor was approximately three times higher in ACS patients than the general population.[8] Data from a retrospective trial of 12,785 patients who underwent percutaneous coronary intervention (PCI) revealed that cancer survivors accounted for a high proportion of PCI patients (one in every 13 patients).[9]

Cancer survivors with CAD have poor prognosis even after receiving the optimal medical therapy and PCI. Yusuf et al[10] found that the one-year estimated survival rate of cancer patients with non-ST elevation myocardial infarction (non-STEMI) was only 26% after medical treatment or PCI, while that of cancer patients with ST elevation myocardial infarction (STEMI) was 22%. Overall survival was even worse in patients with a history of lymphoma/leukemia, chest radiotherapy, chemotherapy, and advanced cancer. The BleeMACS study was a multicenter observational registry involving patients with ACS undergoing PCI. In this study, cancer patients accounted for 6.4% of all the enrolled patients, and cancer was the strongest independent predictor of death and re-infarction ($HR = 2.1$), and bleeding ($HR = 1.5$).[11] Notably, CAD in cancer patients does not often result from the toxicity of cancer therapy, and it may be related to aging or an exacerbation of the underlying cardiovascular disease. Thus, early identification and management of CAD in cancer patients are critical for maintaining the survival benefits of modern cancer therapy.

Common risk factors and pathogeneses between cancer and CAD

Common risk factors

Growing evidence has indicated that cancer and CAD share common risk factors, including obesity, diabetes, hypertension, hyperlipidemia, smoking, inactivity, and unhealthy diet. Obesity is associated with multiple cancers, and every 5% increase in body mass index increases the risk of thyroid, esophageal, endometrial, and gallbladder cancers by 33%−59%.[12] A study comprising of 2943 patients with breast cancer found that an increase in visceral or intramuscular adiposity was associated with the risk of cardiovascular disease (CVD).[13] Obesity is accompanied by insulin resistance, atherogenic dyslipidemia, and inflammation, which contribute to the occurrence of cancer and CAD. Diabetes is considered to be one of the most important risk factors for CVD and has been established as a risk factor for breast cancer. Besides insulin resistance and lipid metabolism disorders, hyperglycemia may also lead to intestinal flora disorder for the induction of inflammation, ultimately promoting carcinogenesis and tumor progression.[14]

Hypertension and dyslipidemia are related to the development of cancers. Compared to normotensive patients, the risk of renal cancer was increased by 94% in patients with a systolic blood pressure >160 mmHg and 75% in those with a diastolic blood pressure >90 mmHg.[15] By examining 244 breast cancer patients, Rodrigues et al[16] found that compared to patients with lower LDL cholesterol (<117 mg/dL), patients with higher LDL cholesterol had significantly larger tumor volume and lower survival rate. The cholesterol metabolite, 27-hydroxycholesterol, was also proven to induce the proliferation and metastasis of breast cancer cells in an experimental mouse model.[17] Smoking and drinking have also been linked to the occurrence of cancers. Smoking may produce carcinogens (benzopyrene and nitrosamine), proinflammatory substances, and oxidation to facilitate tumorigenesis while drinking significantly increases the risk of esophageal, oral, throat, and breast cancers and cancer-related mortality.[18]

In addition, active physical exercise and a healthy diet can improve cellular immune function, maintain energy metabolism, and prevent tumorigenesis.[19] Compared to individuals that performed less exercise, the risk of esophageal cancer, liver cancer, and lung cancer was found to be respectively reduced by 42%, 27%, and 26% in individuals that participated in regular exercise.[20] The Framingham risk scale (FRS)-predicted 10-year risk of CVD was reduced by 11% in persons that participated in aerobic and resistance exercise.[21] Based on the effects of diet on cancer, the intake of vegetables and fruit per day was found to reduce the risk of cancer,[22] and low-carbohydrate diet was positively associated with cancer mortality ($RR = 1.08$).[23] Besides, substituting red meat and processed meat protein with plants to serve as the

protein source can reduce cancer-related ($HR = 0.61$) and CVD-related ($HR = 0.58$) mortality.[24]

Common pathogenesis

The role of inflammation and oxidative stress in atherosclerosis has been previously established.[25] A cohort study of 7178 patients with stable CAD found that chronic systemic low-grade inflammation (C-reactive protein (CRP) ≤10 mg/L) was related to the incidence of cancer (HR = 1.35) during the 12-year follow-up.[26] The CANTOS trial comprising of 10,061 patients with pre-existing myocardial infarction found that patients treated with canakinumab, a therapeutic monoclonal antibody targeting the inflammatory cytokine, IL-1b, had a lower rate of recurrent cardiovascular events than placebo patients. More importantly, canakinumab led to a significant decrease in lung cancer incidence, lung cancer death, and total cancer mortality.[27,28] Oxidative stress and reactive oxygen species are involved in the pathological process of cancer. The activity of Zn-superoxide dismutase (SOD) is highly elevated in patients with colorectal cancer.[29] Additionally, chronic inflammation may induce oxidative stress, facilitating the development of cancer and CAD. The common risk factors and the pathogenesis between cancer and CAD are shown in Fig. 1.

Cancer therapy-induced CAD

Approximately 50% of the cardiovascular toxicity caused by anticancer therapy is presented as vascular injury, which increases the risk of CAD. All types of cancer therapies contribute to the development of CAD, including chemotherapy, radiotherapy, and targeted drug therapy. The pathophysiological mechanisms of myocardial ischemia related to cancer therapy are summarized in Table 1.

Fluorouracil drugs

Fluorouracil is widely used in the treatment of digestive tract tumors and other solid tumors. 5-fluorouracil and its oral pro-drug capacitance are notoriously associated with myocardial ischemia, and the occurrence rates can be as high as 68% and 9%, respectively.[30] The underlying mechanisms of cardiotoxicity induced by fluorouracil are associated with coronary artery vasospasm, vascular endothelial injury, direct cardiotoxic effects, and thrombogenicity.[31] The reported incidence of coronary spasm caused by fluorouracil ranges from 1% to 68%.[32] In addition, 5-fluorouracil is a radiosensitizer that increases the risk of radiation-induced thrombosis.[33] Lestuzzi et al[34] examined 358 cancer patients administered 5-fluorouracil. As a result, they found that 5.9% of patients had rest ischemia. Among those patients, 228 underwent the treadmill exercise test, which revealed that the rate of effort induced myocardial ischemia was approximately 6.9%. Angina and ischemic ECG changes usually occur within a few days after 5-fluorouracil administration, and sometimes may persist following treatment cessation. The propensity of 5-fluorouracil to induce acute myocardial infarction has been well established,[35] and people with cardiovascular risk factors, such as smoking, hypercholesterolemia, and diabetes, are more likely to suffer from cardiotoxicity induced by this drug. Calcium channel blockers and nitrates are used in high-risk patients to prevent and treat coronary artery spasm caused by 5-fluorouracil.[36] However, coronary spasm may recur after 5-fluorouracil administration due to the limited effects of this vasodilator.

Platinum drugs

Platinum drugs are effective therapies for numerous solid tumors such as ovarian cancer, lung cancer, and testicular cancer; however, they increase the risk of adverse cardiovascular events. The long-term risk of CAD is 1.5−7.0 times higher in patients receiving platinum-based chemotherapy than controls.[37−40] Cisplatin has been reported to be closely associated with acute coronary thrombosis, and even multiple coronary thrombi may occur after cisplatin treatment.[41] Approximately 2% of patients treated with cisplatin suffer from myocardial ischemia due to arterial thrombosis.[42] The proposed mechanisms underlying the cardiotoxicity induced by platinum drugs are direct endothelial toxicity, platelet activation and aggregation, and thrombogenesis.[43−45] In a study with testicular cancer survivors, compared to patients receiving surgery alone, those administered cisplatin were found to have a significant increase in the risk of CAD ($HR = 2.6$) during the 20-year follow-up.[46] Moore et al[42] also observed that 18.1% of patients treated with cisplatin had venous and arterial thromboembolic events.

Immune checkpoint inhibitors

Programmed death molecule 1 (PD-1) and cytotoxic T lymphocyte-cell associated antigen 4 (CTLA-4) are

Table 1
Pathophysiological mechanisms of CAD related to cancer therapy.

Agents	Pathophysiological mechanism	Risk of myocardial ischemia
Fluorouracil drugs (5-fluorouracil and capecitabine)	• Coronary spasm • Vascular endothelial injury • Direct cardiotoxic effects • Thrombogenicity	• Up to 68% myocardial ischemia with 5-fluorouracil and 9% with capacitance • 5.9% of patients have rest ischemia • 6.9% of patients have effort induced myocardial ischemia
Platinum drugs (Cisplatin)	• Direct endothelial toxicity • Platelet activation and aggregation • Thrombogenesis	• 1.5−7.0 folds increase in long-term risk of CAD
Immune checkpoint inhibitors	• Plaque formation • Plaque rupture	• The incidence of myocardial infarction is 1%
Radiotherapy	• Vascular endothelial injury • Plaque rupture • Thrombosis formation • Coronary spasm • Microvascular dysfunction	• The incidence of CAD is linear with the mean cardiac dose of radiotherapy, increasing by 7.4% per Gy • 4- to 6-fold increase in the risk of CAD in patients received mediastinal radiotherapy
Targeted drug therapy	• Vascular endothelial injury • Plaque rupture • Arterial thrombosis • Microvascular dysfunction	• 2 to 6 times greater risk of ACS with VEGF inhibitors • Arterial thrombosis: sorafenib 1.7%, sunitinib 1.4%

ACS: acute coronary syndrome; CAD: coronary artery disease; VEGF: Vascular endothelial growth factor.

major immune checkpoints that can prevent the over-activation of the human immune system and avoid the occurrence of autoimmune diseases. Under the stimulation of the tumor microenvironment, the immune checkpoint pathway is over-activated, leading to immune escape.[47] Immune checkpoint inhibitors significantly improve the prognosis of many cancers, but also increase the risk of CAD.[48] Immune checkpoint inhibitors play a critical role in atherosclerosis by regulating the activation and proliferation of T cells, macrophages, and platelets.[49] Immune checkpoint inhibitors can contribute to the formation and rupture of unstable atherosclerotic plaques by inducing different inflammatory cytokines and atherosclerotic cytokines related to overactivated T cells.[50] A meta-analysis showed that the incidence of myocardial infarction was approximately 1% in cancer patients treated with immune checkpoint inhibitors.[51]
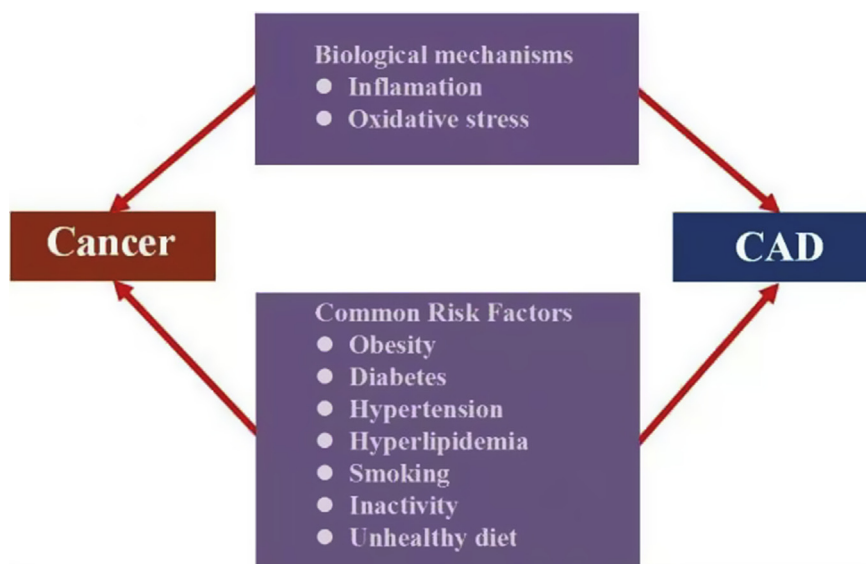

Fig. 1. Common risk factors and pathogenesis between cancer and coronary artery disease.

Radiotherapy

Radiotherapy is considered to be the primary treatment for solid tumors and hematological malignancies. Thus, more than 50% of cancer patients have been administered this therapy. Numerous studies have confirmed that radiotherapy can damage vascular endothelial cells, and this is followed by plaque rupture and thrombosis formation, which might be accompanied by coronary spasm, ultimately causing CAD.[52] Radiotherapy leads to the formation of cholesterol plaques and thrombosis within a few days in experimental models.[53,54] Radiotherapy on the left breast or chest often impairs the left anterior descending branch and diagonal branch, especially the ostium of the vessel. Besides, fibrosis occurs in all three layers of the vascular wall followed by accelerated atherosclerosis.[55,56] In addition to macrovascular disease, radiotherapy results in microvascular dysfunction, causing the reduction of coronary flow reserve (CFR) and myocardial ischemia. CAD usually appears after more than 10 years of radiotherapy, and young patients with curable malignancies suffer the most from radiation-induced cardiotoxicity. CAD has been found in nearly 20% of young people receiving radiotherapy with 20 as the average age.[57] Mediastinal radiation for Hodgkin disease and left-sided breast cancer are the main factors that lead to a greater propensity toward CAD in young cancer patients. In a retrospective study of 2524 survivors of Hodgkin's lymphoma, Van Nimwegen et al[58] found that compared to the non-mediastinal radiotherapy group, the mediastinal radiotherapy group had a 4- to 6-fold increase in the risk of CAD. A chest radiation dose greater than 30 Gy was also previously proven to cause cardiovascular injury.[59] Individuals with cardiovascular risk factors are more susceptible to CAD induced by radiotherapy.[60] By analyzing 3964 Hodgkin lymphoma patients with pre-existing heart disease, Myrehaug et al[61] concluded that a prior history of heart disease was the strongest predictor of cardiac toxicity after radiotherapy ($HR = 3.98$, $P < 0.001$).

Targeted drug therapy

Targeted drugs kill cancer cells by specifically binding to carcinogenic sites without affecting the biological function of peripheral normal cells. However, many targeted therapies, especially monoclonal antibodies and tyrosine kinase inhibitors, have been demonstrated to interfere with the cell signaling pathway closely related to CAD.[62] Vascular endothelial growth factor (VEGF) inhibitors, which are a type of chemotherapeutics for multiple solid tumors, predispose patients to the increased risk of thrombosis. In fact, patients treated with the VEGF pathway inhibitors are at a 2 to 6 times greater risk of ACS.[63,64] Compared to chemotherapy alone, the incidence of arterial thromboembolism is significantly increased with the combination of bevacizumab and chemotherapy ($HR = 2$).[65] The incidence of arterial thromboembolism is 1.7% in patients treated with sorafenib and 1.4% in those treated with sunitinib. A decrease in CFR occurs in 72% of patients receiving sunitinib therapy, especially in patients administered long-term treatment.[66] Sunitinib also contributes to microvascular dysfunction[67] and the simultaneous rarefication of microvascular pericytes and capillaries in the laboratory.[68] Sorafenib was reported to induce vasospasm and impair multiple vessels at a rate that is more profound than that of sunitinib.[69−71] Besides, sorafenib contributes to the progression of CAD and atherosclerotic plaque rupture by impairing endothelial healing.[72] Nilotinib and ponatinib have been found to be associated with the progression of atherosclerosis.[73,74]

Diagnosis of CAD in cancer patients

Typical chest pain is usually absent in cancer patients with CAD. However, dyspnea is the principal clinical manifestation, resulting from analgesic treatment or neurotoxicity of radiotherapy and chemotherapy. Only 30.3% of cancer patients have chest pain and 44% of those with CAD have dyspnea.[10] However, its atypical clinical presentation poses a great challenge when CAD is being diagnosed in cancer patients. The assessment and examination of myocardial ischemia are thus key to diagnosing silent CAD. If cancer patients have dyspnea, attention should be paid to the screening of CAD. In fact, symptoms, risk factors, cardiac biomarkers, electrocardiogram (ECG), and anticancer therapy should be assessed according to the ACC and AHA guidelines.[75] Anticancer therapies not only cause coronary artery injury, but also coronary microcirculation dysfunction.[76] If the angina symptom of cancer patients is typical, but abnormality is not evident by coronary CT angiography (CCTA) or coronary angiography, coronary microcirculation resistance index or myocardial contrast echocardiography (MCE) should be performed.

Approximately 10% of cancer patients with ACS have takotsubo cardiomyopathy, and most are treated with 5-fluorouracil, capecitabine, cytarabine, axitinib, sunitinib,

bevacizumab, rituximab, trastuzumab, or combretastatin.[77] The prevalence of cancer is also high (23.7%) in patients with takotsubo cardiomyopathy.[78] Early identification of takotsubo cardiomyopathy can prevent the risk of bleeding caused by antithrombotic treatment.[79] Takotsubo cardiomyopathy can be diagnosed according to the Mayo Center diagnostic criteria: (a) weakened left ventricular middle wall motion, dyskinesia or no movement with or without apical wall motion abnormalities; the range of the wall motion abnormalities should be larger than that of a single coronary artery distribution, and stress stimulus factors often occur simultaneously; (b) no evidence of coronary artery stenosis or plaque rupture; (c) new ECG changes (ST segment elevation or T wave inversion in precordial leads); and (d) no pheochromocytoma, myocarditis, or other diseases, leading to left ventricular dysfunction.

Cancer-related CAD should be distinguished from Kounis syndrome (KS), which is defined as a special type of ACS that occurs secondary to allergic reaction by inflammatory mediators mainly released from activated mast cells.[80,81] Anticancer agents have hapten characteristics. As previously reported, approximately 42% of patients display hypersensitivity reaction, 2% have severe allergy after paclitaxel treatment, and 19.27% of patients treated with capecitabine, oxaliplatin, or bevacizumab have allergic reactions. There are 3 types of KS according to the different pathogeneses: Type I, ACS secondary to coronary spasm in patients without underlying CAD; Type II, ACS secondary to coronary spasm or plaque rupture in patients with underlying CAD; and Type III, ACS secondary to coronary thrombosis, including stent thrombosis. KS can be diagnosed according to the following criteria: (a) ACS after infusion of anticancer drugs that may cause allergy; (b) symptoms, signs, and laboratory findings of acute allergic diseases; (c) eosinophils and mast cells identified through histological examination of thrombus; and (d) exclusion of other diseases (such as thrombophilia, systemic lupus erythematosus (SLE), and polycythemia). Besides the above diseases, others that must be excluded when considering cancer-related CAD include myocarditis, pericarditis, and pulmonary embolism.

Cardiovascular imaging for the detection of CAD in cancer patients

Cardiovascular imaging is required for the diagnosis and therapeutic monitoring of CAD in cancer patients and echocardiography is primarily used to examine cardiac function and structure. As CAD patients often exhibit normal wall motion, except for critical ischemia or myocardial infarction, normal resting echocardiography may not exclude the possibility of CAD. Thus, stress echocardiography has a great sensitivity and specificity for CAD diagnosis, especially in patients with negative exercise ECG.[82,83]

CCTA is broadly used as an ideal imaging modality to evaluate suspected patients with CAD. As most cancer patients may suffer from silent ischemia, CCTA may be used as an effective tool to assess coronary arteries, despite the lack of typical symptoms.[84] CCTA can also improve the accuracy of CAD estimation for asymptomatic patients by using the coronary artery calcification score.[85] However, further large-scale trials are needed to explore the feasibility of CCTA in predicting long-term cardiovascular outcomes.[86] Currently, coronary angiography remains the "gold standard" for diagnosing CAD.

Cardiac MRI can detect CAD and accurately quantify the degree of ischemia. Theoretically, cardiac perfusion MRI may be used to detect the insufficiency of myocardial perfusion during or after anticancer therapy.[87] Positron emission tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) are also used to assess myocardial perfusion abnormalities for the diagnosis, risk stratification, and therapy guidance of cancer patients with suspected CAD.[88]

Biomarkers for the detection of CAD in cancer patients

Specific biomarkers are particularly important in the early identification and progression monitoring of CAD in cancer patients. Thus, several cardiac biomarkers have been examined in the field of cardio-oncology. A 7-year follow-up study of breast cancer patients undergoing radiotherapy revealed that B-type natriuretic peptide (BNP) levels were related to radiation doses, but were irrelevant to the onset of CAD.[89] A prospective study comprising of 555 patients with cancer as their primary diagnosis showed that the serum level of high-sensitive troponin T was increased in cancer patients before the initiation of any cardiotoxic anticancer therapy, and was strongly related to advanced cancer stage and all-cause mortality.[90] A cohort study also found that troponin I was increased in cancer patients shortly after high-dose chemotherapy, indicating that it can be used as a strong predictor of poor cardiac outcome in cancer patients receiving high-dose chemotherapy.[91] Other biomarkers of cardiotoxicity, including myocardial ischemia markers (heart-type fatty acid binding protein [H-FABP] and

glycogen phosphorylase isoenzyme BB [GPBB]), and inflammatory and oxidative stress markers (Interleukin, high-sensitivity C-reactive protein [hs-CRP], and glutathione peroxidase) have been reported to be significantly changed during chemotherapy in small-sample studies.[92,93] As H-FABP and GPBB change 2–4 h after myocardial injury, they are considered to be sensitive early biomarkers for cardiotoxicity. GPBB can also be used for risk stratification in cancer patients with CAD as it is independently associated with mortality[94] while hs-CRP is a risk factor for CVD and cancer. A retrospective study involving 2867 stable CAD patients undergoing PCI suggested that hs-CRP was closely related to the higher risk of cancer death.[95] However, further research is needed to accurately evaluate the predictive value of these cardiac biomarkers in cancer patients.

Screening for CAD in cancer survivors

After anticancer therapy, the risk of CAD is considerably increased in cancer patients. Thus, growing emphasis has been placed on the identification of cancer survivors who are most vulnerable to CAD. However, more effective evaluation measures are required for early detection of cardiotoxicity to optimize the cardioprotective strategies and enhance personalized medical therapy. Identifying patients with pre-existing CAD and cardiovascular risk factors is critical before the initiation of anticancer therapy. The patient's history of CVD should also be acquired before initiating potentially cardiotoxic anticancer therapy; high-risk factors of CAD should be screened; and the patient's treatment process (e.g., cumulative dose of chemotherapy and radiotherapy) must be recorded in-depth. The risk of recurrent and secondary malignant tumors and adverse cardiovascular events are markedly increased in cancer survivors. Therefore, regular annual follow-up of high-risk individuals, such as survivors of Hodgkin's lymphoma, is recommended according to the Clinical Practice Guidelines for Oncology (NCCN).

The best time to initiate the surveillance of cardiotoxic manifestations remains unclear due to the divergent opinions of experts and the lack of official guidelines. Patients with a history of systemic radiotherapy, cardiotoxic chemotherapy, total mediastinal radiotherapy ≥20 Gy, and combined chemotherapy are at a high risk of developing cardiotoxic events, and they are recommended to have an annual follow-up and physical examination by the Children's Oncology Group.[96] For patients who receive a total anthracycline dosage of 300 mg/m^2 or chest radiation on both sides, an annual serial ECG is recommended. Serial ECG can be performed every 2–5 years for patients at lower risk. Asymptomatic patients at high risk should undergo stress testing and echocardiography for surveillance of CAD 5–10 years after anticancer therapy. If no new symptoms arise, a reassessment every 5 years is recommended.[97] CCTA is superior to functional stress tests for assessing the coronary artery. Ultimately, coronary angiography remains the best method to detect CAD, and imaging modalities and functional tests should be considered if necessary. In 2016, the Society of Cardiovascular Angiography Intervention (SCAI) guidelines[98] proposed that patients undergoing chemotherapy or radiotherapy should perform CCTA every 5 years, especially in high-risk populations. Irradiated patients who are older than 60 years with one or more cardiovascular risk factors or established CAD, should reexamine CCTA 2 years after treatment.

Management of CAD in cancer patients

As the health condition of cancer patients is complex and changeable, the management of CAD in cancer patients needs multidisciplinary cooperation to formulate a reasonable and individualized plan.

Special considerations with anticancer therapy

The risk of myocardial ischemia caused by fluorouracil and capecitabine is relatively high; thus, patients with angina should exercise caution when taking these drugs and myocardial ischemia should be closely monitored via regular ECG and cardiac biomarkers. Once symptomatic ischemia occurs, the drugs should be immediately terminated. Anthracycline drugs should also be used with caution in patients with myocardial infarction or heart failure. Imaging tests and monitoring with cardiac biomarkers are also recommended. In cancer patients with unstable or acute decompensated heart diseases (e.g., ACS or heart failure), temporary cessation of anticancer therapy with cardiotoxicity should be considered. For patients with old myocardial infarction and compensated cardiac function, if the cardiotoxic anticancer therapy is the first-line treatment, communicating with patients and obtaining informed consent are crucial before application. Additionally, patients should be closely monitored. Reducing the dosage of radiation therapy and chemotherapeutic agents, or switching to less cardiotoxic chemotherapy drugs aids in reducing cardiotoxicity.

Pharmacotherapy

Cancer patients with stable angina prefer to receive drugs that can relieve angina and improve tumor prognosis. Many agents are reported to have cardioprotective effects in the laboratory; however, whether those agents can alleviate the cardiac symptoms induced by chemotherapy and radiotherapy remain unclear. Agents, such as aspirin, beta-blockers, statins, and angiotensin antagonists, have been demonstrated to be cardioprotective in cancer patients. Among those agents, aspirin and beta-blocker are beneficial for cancer patients even after adjustments are made for confounders.[99] An analysis of 456 cancer patients with acute myocardial infarction showed that long-term aspirin (*HR* = 0.77) and beta blocker (*HR* = 0.64) treatment significantly reduced mortality.[100] Further, a Danish study indicated that cancer-related mortality was significantly lower in long-term statin users compared to non-statin users (*HR* = 0.85).[101] Raebel et al[102] found that hypertensive patients taking angiotensin converting enzyme inhibitors had a significantly lower risk of breast cancer (*HR* = 0.55) than patients taking calcium channel blockers. Metformin was reported to reduce the risk of multiple cancers, including gastric cancer, lung cancer, and breast cancer.[103−105] A dose-dependent association was found between the use of hydrochlorothiazide and the increased risk of squamous cell carcinoma.[106] The cumulative hydrochlorothiazide dose >200,000 mg increases the risk of basal cell tumors by 54% and squamous cell carcinoma by 6-fold.[107] Besides the above drugs, the use of insulin glargine is associated with an increased risk of breast cancer in women with type 2 diabetes.

PCI

Generally, cancer patients with stable CAD should receive medical therapy as the first treatment. When angina (CCS III or IV) is present despite the optimal medical therapy, revascularization therapy should be considered in stable patients. Importantly, the severity of CAD, malignant tumor staging, and patient status should be considered when exploring revascularization strategies.[108] The minimally invasive procedure, PCI, is the preferred revascularization strategy for most cancer patients with CAD, especially if their malignancy is aggressive or widespread. Furthermore, if STEMI or high risk non-STEMI occurs in cancer patients with an expected life span of <1 year, PCI should also be considered.[109] A lower mortality rate was found among cancer patients undergoing PCI

regardless of cancer types. In addition, a study comprising of 49,515 cancer patients with ACS found that the in-hospital mortality rate of patients undergoing PCI was significantly lower than that of patients receiving conservative medical therapy.[110] Thus, hemoglobin, platelet count, and coagulation tests should be timely assessed in cancer patients before PCI. Cancer patients diagnosed within 6 months prior to ACS presentation appear to have the highest risk of mortality among all patients. They are also more susceptible to hemodynamic disorder and often need hemodynamic support.

Thrombocytopenia has been identified in most patients with acute leukemia, lymphoma, and multiple myeloma. However, 10%−25% of patients with solid tumors after chemotherapy may also have this condition[111] and because of the effects of chemotherapy, hypohemoglobin is also possible.[112] If thrombocytopenia and hypohemoglobin occur simultaneously, the cessation of antiplatelet and invasive therapy would be required. Although thrombocytopenia cannot prevent the development of myocardial ischemia in cancer patients, it can contribute to thrombus formation.[113,114] Therefore, thrombocytopenia is not an absolute contraindication for intervention therapy. When platelet count is > 50,000/mL and coagulation abnormality does not occur, the standard dose of heparin (50−70 U/kg) or bivalirudin can be used as the anticoagulation treatment during PCI; however, if platelet count is < 50,000/mL, the initial dose of heparin should be reduced (30−50 U/kg) and an additional heparin dose be added when ACT is less than 250 s during the procedure.[115,116] Currently, preventive platelet transfusion is not recommended; instead, it should be considered when: (a) platelet count is < 20,000/mL with at least one of the following situations (high fever, leukocytosis, rapid decrease of platelet count, and other abnormal coagulation function); and (b) patients with solid tumors have a platelet count <20,000/mL. Therapeutic platelet transfusion is only recommended in thrombocytopenia patients who develop bleeding during or after cardiac catheterization.

Radial access is the primary choice for PCI as it reduces bleeding complications. However, femoral artery access is the preferred choice for patients that fail both arms of the Allen's test, are on regular hemodialysis, and have undergone bilateral mastectomy.[117] Moreover, balloon dilatation alone is preferred for patients requiring cancer surgery in the near future, and stent placement can be performed after the surgery, if necessary. To prevent the increased risk of bleeding from long-

term dual antiplatelet therapy (DAPT), bare metal stents are preferred; however, the risk of restenosis is higher with the stents.[118] Currently, the duration of DAPT can be remarkably shortened following the implantation of the new generation of drug eluting stents (DES). Therefore, it is recommended that the new generation DES[119] be selected for cancer patients. However, drug coated balloon (DCB) can also be attempted to shorten the DAPT duration in some patients. Intravascular imaging, including intravascular ultrasound (IVUS) or optical coherence tomography (OCT), should be performed to optimize PCI, and sometimes, functional tests, including flow fraction reserve (FFR) and instant flow reserve (iFR), should be performed to determine the hemodynamic relevance of coronary artery stenoses in cancer patients. As anticancer therapy often leads to an impaired immune system, vascular closure devices should be avoided in cancer patients to prevent local infection.[120] However, rotational atherectomy is recommended for severe calcified lesions.

The current SCAI consensus for cancer patients with CAD provides the following recommendations: aspirin administration when platelet count is >10,000/mL; DAPT with aspirin and clopidogrel administration if platelet count is >30,000/mL; and the administration of the new potent ADP receptor antagonists, such as ticagrelor and prasugrel, only when platelet count is >50,000/mL.[121] Previously, we found that a half dose of ticagrelor exhibited the same antiplatelet effect as its standard dose,[122] and 1/4 of its standard dose displayed a significantly better antiplatelet effect than the standard dose of clopidogrel.[123] Therefore, the dosage of new antiplatelet drugs should be reduced in cancer patients with CAD, but the optimal dosage must be confirmed via future studies.

Generally, PCI is safe in cancer patients with a platelet count >50,000/mL; however, balloon dilatation alone, bare metal stent (BMS), DCB, and the new generation DES are the preferred choices of treatment. DAPT duration can be appropriately shortened in cancer patients with a high risk of bleeding after PCI. However, for patients that undergo balloon dilatation alone, BMS implantation or DCB, and the new generation DES implantation, DAPT should be administered for 2 weeks, 4 weeks, and 6 months, respectively, if platelet count is <50,000/mL and optimal stent expansion has been confirmed by IVUS or OCT.[124] Intravascular imaging modalities and functional tests aid in PCI optimization. If the endothelialization of stents is delayed and the risk of stent thrombosis is increased by active chemotherapy, prolonging DAPT for an appropriate duration may be considered. After PCI, the antithrombotic therapy administered to cancer patients using cisplatin and thalidomide should be strengthened because of the pro-thrombosis effects.

Coronary artery bypass grafting (CABG)

For cancer patients displaying good survival and are appropriately indicated, CABG should be considered to reduce the accompanied cardiac complications during or after noncardiac surgery. Additionally, the stage of cancer and the general health condition of the patient are important considerations prior to CABG. CABG can be simultaneously performed with lung cancer surgery via the same incision.[125,126] The simultaneous performance of CABG and tumor resection is beneficial as repeated thoracotomy is avoided, which leads to reduced complications and hospitalization costs. However, to avoid the risk of mediastinitis, the resection of gastrointestinal tumors should not be simultaneously performed with CABG.[127] CABG may be difficult in patients administered radiotherapy as they have a high incidence of mediastinal fibrosis. Because of this condition, the use of internal mammary artery as a bridging vessel should be avoided in patients administered radiotherapy.[128]

Conclusions

Cancer and CAD share some common risk factors. In addition, they have the same underlying pathogenesis. Although substantial advancements have been made in cancer treatment, the number of cancer patients with concomitant CAD has been increasing. Owing to the complex condition of these patients, it is imperative that the oncology department and cardiovascular department work together to derive optimal specialized cardiac care for patients. Moreover, current guidelines are not suited for cancer patients with CAD. Thus, both basic and clinical research are required to develop diagnostic and therapeutic guidelines for cancer patients with CAD.

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Conflict of interest

None.

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