Review article

Cardio-oncology: a multidisciplinary approach for detection, prevention and management of cardiac dysfunction in cancer patients

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Abstract

Cardiac dysfunction that develops during or after completion of cancer therapy is a growing health concern that should be addressed in a multidisciplinary setting. Cardio-oncology is a new discipline that focuses on screening, monitoring and treating cardiovascular disease during and after cancer treatment. A baseline cardiovascular risk assessment is essential. For high-risk patients, a tailored and detailed plan for cardiovascular management throughout treatment and beyond should also be established. Anthracycline and/or trastuzumab-containing chemotherapy and chest-directed radiation therapy are well known cardiotoxic cancer therapies. Monitoring for the development of subclinical cardiotoxicity is crucial for the prevention of clinical heart failure. Detecting a decreased left ventricular ejection fraction after cancer therapy might be a late finding; therefore, earlier markers of cardiac injury are being actively explored. Abnormal myocardial strain and increased serum cardiac biomarkers (eg, troponins and natriuretic peptides) are possible candidates for this purpose. An important method for preventing heart failure is the avoidance or minimization of the use of cardiotoxic therapies. Decisions must balance the antitumor efficacy of the treatment with its potential cardiotoxicity. If patients develop cardiac dysfunction or heart failure, they should be treated in accordance with established guidelines for heart failure. Cancer survivors who have been exposed to cardiotoxic cancer therapies are at high risk of developing heart failure. The management of cardiovascular risk factors and periodic screening with cardiac imaging and biomarkers should be considered in high-risk survivors.

Introduction

Cardio-oncology is a new discipline that focuses on screening, monitoring and treating patients with heart disease during and after cancer treatment (1). It is a multidisciplinary field that requires oncologists and cardiologists to be brought together to provide short- and long-term cardiovascular (CV) care for cancer patients and survivors. Cardiac dysfunction and heart failure (HF) are well-recognized complications that impact the survival and quality of life in cancer patients. In this document, we discuss the different steps in cardio-oncological approach for CV monitoring and decision-making before, during and after cancer treatment with potential cardiac dysfunction.

1. Baseline cardiovascular evaluation

A baseline CV risk assessment is important prior to the initiation of cancer therapy. For high-risk patients, a tailored and detailed plan for CV management throughout treatment and beyond should also be established. The first step in the identification of higher risk patients for cardiotoxicity consists of a history and physical examination and a screening for CV risk factors. Unfavorable lifestyle choices (e.g., smoking, overweight, reduced physical activity) have been known to increase the risk of cardiotoxicity (2,3). Patients with pre-existing comorbidities (e.g., hypertension, diabetes, angina, HF) or previous histories of coronary bypass, stroke or thromboembolic events should receive particular attention during the course of anticancer therapy because their risk of developing adverse events due to cardiotoxicity is elevated (4). Blood hematochemical parameters should be measured together with blood pressure tests, electrocardiogram (ECG) and echocardiogram. Patients with poorly controlled hypertension, severe arrhythmias and left ventricular (LV) ejection fraction (LVEF) less than 50% are at high risk for cancer therapy-induced cardiotoxicity (4). This assessment of the CV profile should then be taken into consideration by the oncologist in deciding the therapeutic

approach, in terms of drug selection and schedule, for each individual patient **(Figure 1)**. Recently, the American Society of Clinical Oncology released a guideline for the prevention and monitoring of cardiac dysfunction in survivors of adult cancers (5). The guideline recommends that cancer patients who receive the following treatment should be considered at high risk for developing cardiac dysfunction (5):

1) Treatment that includes any of the following:
   - High-dose anthracycline (e.g., cumulative doxorubicin dose ≥ 250 mg/m^2, cumulative epirubicin dose ≥ 600 mg/m^2)
   - High-dose radiotherapy (≥ 30 Gy) where the heart is in the treatment field
   - Lower-dose anthracycline in combination with lower-dose radiotherapy where the heart is in the treatment field
2) Treatment with lower-dose anthracycline or trastuzumab alone and the presence of any of the following risk factors:
   - Multiple (≥ 2) CV risk factors, including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
   - Older age (≥ 60 years) at cancer treatment
   - Compromised cardiac function (e.g., LVEF 50% to 55%, a history of myocardial infarction, ≥ moderate valvular heart disease) at any time before or during treatment
3) Treatment with lower-dose anthracycline followed by trastuzumab.

It should be noted that the target populations of this guideline are not Japanese cancer patients. Thus, careful consideration should be given to applying the guideline for Japanese patients.

2. Cardiovascular monitoring during cancer treatment

Left ventricular ejection fraction

A drop in LVEF has been mostly used as a marker of cardiotoxicity. In many clinical studies,

cardiotoxicity was defined as a reduction in LVEF by more than 10 percentage points from baseline and < 50% (6,7). LVEF is one of the most important predictors of prognosis; patients with substantially reduced ejection fractions typically have a poorer prognosis (8).

Echocardiography, nuclear imaging and magnetic resonance imaging (MRI) are used for the measurement of LVEF. Of these, 2-dimensional (2-D) echocardiography is the most commonly used imaging technique to monitor LVEF during and after chemotherapy. It is a widely available, reproducible, noninvasive modality that permits safe and serial assessment of cardiac function. However, intra- and inter-observer variability is a major limitation (9). In contrast, 3-D echocardiography has been shown to be the preferred technique for monitoring LVEF and is more reproducible in cancer patients (10). Nuclear imaging also can limit inter-observer variability in assessing LVEF, but it has the disadvantages of exposing patients to radiation and providing limited information on cardiac structure (11). The cardiac MRI might be useful for the noninvasive assessment of LV volumes and LVEF in the cancer setting. In addition to accurate and highly reproducible determination of LV volumes and systolic function, cardiac MRI is also useful for the detection of myocardial edema, perfusion abnormalities and fibrosis (2). However, because of the high cost and lack of availability, it is not routinely used.

Although LVEF remains the most commonly accepted parameter of systolic function, it has shown low diagnostic sensitivity and low predictive power in detecting a subclinical myocardial injury (8). When a drop in LVEF is detected in cancer patients, they would have incurred irreversible myocyte damage by that stage (12). For this reason, earlier markers to detect subclinical cardiac toxicity have been in great demand.

Myocardial strain

An echocardiographic myocardial strain analysis using 2-D speckle tracking imaging is a

promising candidate for the detection of early cardiotoxicity. Global longitudinal strain (GLS) can be a useful early marker that is predictive of a further decrease in LVEF (13). The ideal cutoff value to define a clinically relevant change in strain values remains unclear. A 10% to 15% early reduction in GLS during cancer therapy appears to be the most useful parameter for the prediction of cardiotoxicity (13). Thus, the myocardial strain seems to be a useful parameter for the early detection of cardiotoxicity. However, there are currently important limitations: its data analysis is time-consuming and depends on the quality of the acoustic windows, and different echo machines and software packages may yield different strain results, thereby making them difficult to compare (14).

Serum markers

Serum markers that detect damage of cardiomyocytes, such as troponin I or T, are useful in detecting acute cardiotoxicity (15). B-type natriuretic peptide (BNP), which is a cardiac neurohormone specifically secreted from the cardiac ventricles as a response to increased wall tension, may be used as a biomarker. However, there is still an insufficient amount of definitive evidence regarding a diagnostic or prognostic role in predicting chemotherapy-induced cardiomyopathy (8).

3. Management of cardiotoxicity

The primary goal is to prevent symptomatic HF and deliver optimal cancer therapy. The American College of Cardiology (ACC)/American Heart Association (AHA) identifies 4 stages of HF. Stage A identifies patients who are at high risk for developing HF but have no structural heart change; stage B refers to patients with structural heart disease but who have never developed symptoms of HF; stage C denotes patients with past or current symptoms of HF associated with underlying structural heart disease; and stage D designates patients with

end-stage HF (16). HF is a progressive disease. That is, once a patient moves to a higher stage, regression to an earlier stage of HF is not observed (16).

3.1. Primary prevention of heart failure

Based on the above classification, every patient receiving cardiotoxic cancer therapy should be considered to be in stage A HF. Therefore, an important method for primary prevention involves the avoidance or minimization of the use of potentially cardiotoxic drugs if established alternatives exist (5). For patients with an indication of radiation therapy (RT), approaches to reduce cardiac radiation exposure using modern RT planning and delivery techniques can lower the risk of HF development (5). Decisions must balance the antitumor efficacy of the treatment with the potential for acute and long-term cardiotoxicity.

For patients planning to receive high-dose anthracyclines, co-administration of the cardioprotectant dexrazoxane or continuous infusion/liposomal formulation of doxorubicin may be an option to reduce the risk of cardiotoxicity, with low probability of compromising cancer-specific outcomes (5). However, there is no evidence to suggest that these approaches would reduce the risk of cardiotoxicity in patients receiving lower-dose anthracyclines.

Prophylactic use of angiotensin-converting enzyme (ACE) inhibitors, β-blockers, or angiotensin receptor blockers (ARBs) for prevention of chemotherapy-induced cardiotoxicity is an ongoing area of active investigation. On the basis of a recent meta-analysis, cardiac events (LV dysfunction and/or HF) were reduced with the prophylactic use of β-blockade (relative risk [RR]=0.31 [95% CI 0.16–0.63], p=0.001) or angiotensin antagonists (RR=0.11 [95% CI 0.04–0.29], p <0.0001) when compared to controls (17). Overall, the evidence in support of primary prevention is quite limited because of a small sample size and variable follow-up and end points. The prophylactic use of these drugs might be an option for cancer patients at a high risk for cardiotoxicity.

The management of CV risk factors is thought to be also important for primary prevention (5). Although no randomized trials have demonstrated that aggressive management of CV risk factors resulted in improvements in long-term cardiac outcomes in cancer survivors, studies in non-cancer populations highlight the importance of vigilance and treatment of these modifiable risk factors (16).

3.2. Treatment of asymptomatic cardiac dysfunction (stage B HF)

If an asymptomatic LVEF reduction is detected, meeting the definition of stage B HF, patients should be treated in accordance with established guidelines (16). Drug therapy should include angiotensin antagonists (ACE inhibitors/ARBs) and β-blockers similar to the general HF (16). More specifically, patients with anthracycline-induced cardiotoxicity can have a better cardiac outcome when treated with ACE inhibitors and/or β-blockers early after the detection of cardiac dysfunction (6,18). Furthermore, the combination therapy may be more effective than either treatment alone (6,18). The time elapsed from the end of chemotherapy to the start of HF therapy can be a crucial variable for the recovery of cardiac function (18). However, there is currently no data to determine whether this HF therapy can be discontinued after achievement of complete recovery of LVEF, or should be prolonged throughout life.

In the setting of cancer therapy-related cardiotoxicity, stage B HF could involve occult LV dysfunction (normal LVEF with abnormal myocardial strain and/or biomarkers) as well as overt LV dysfunction (decreased LVEF) (12). There is little evidence to guide the management of occult cardiotoxicity in stage B HF. Limited data have suggested a benefit from early initiation of ACE inhibitors (7) or β-blockers (19) in patients with troponin I elevation (7) or abnormal myocardial strain (19) without overt LVEF decline.

No recommendations can be made regarding the continuation or discontinuation of cancer therapy in individuals with evidence of cardiac dysfunction (5). A multidisciplinary

discussion about the risks and benefits of further chemotherapy should be undertaken to determine subsequent treatment plans.

3.3. Treatment of symptomatic heart failure (stage C and D HF)

Traditionally, symptomatic HF due to cancer therapy has been believed to be resistant to HF treatment and was associated with a poor prognosis. A study published in 2000 showed that the 5-year survival rate of doxorubicin cardiomyopathy was below 45%, with a hazard ratio of 2.64 relative to idiopathic cardiomyopathy for death or cardiac transplantation over a follow-up of 4.4 years (20). However, recent data showed that in-hospital mortality did not differ among cancer patients with cardiotoxicity compared to other hospitalized HF patients (21). The majority of patients with cancer therapy-related cardiotoxicity received recent guideline-concordant therapies in the USA, including use of ACE inhibitors and β-blockers (21), which may be the reasons for the improvements in HF outcomes in these cancer patients.

If patients develop symptomatic HF, they should be treated in accordance with established guidelines (16). ACE inhibitors/ARBs and β-blockers are key drugs for the treatment of symptomatic HF. Diuretics, aldosterone receptor antagonists and digoxin can be used based on the patient's condition. Cardiac resynchronization therapy (CRT), also known as biventricular pacing, is a relatively new therapeutic approach in advanced HF patients with a reduced LVEF and intraventricular conduction delay (22). Ventricular dyssynchrony can impair ventricular pump function. CRT improves ventricular function by simultaneous pacing of both ventricles to improve electrical (and consequently mechanical) coordination and, therefore, pump efficiency. There have been only a few single-center, small observational studies examining CRT in cancer therapy-induced HF patients (23,24). In a larger study by Rickard et al. (24), 18 patients with anthracycline-induced cardiomyopathy who underwent

implantation of a CRT device were compared with 189 patients with other forms of non-ischemic cardiomyopathy. The authors showed significant improvements in LVEF and symptoms in anthracycline-induced cardiomyopathy patients with CRT. These changes were similar to patients in the non-ischemic cardiomyopathy cohort. Thus, CRT may hold promise for anthracycline-induced HF patients, but it is unclear whether the benefit of CRT can be extended to HF from nonanthracycline chemotherapeutic agents or to all forms of cancer therapy-induced HF. If patients develop stage D HF, patients should be evaluated to determine if the following treatments are available options: heart transplant, ventricular assist devices, continuous infusion of intravenous heart pump drugs, and end-of-life (palliative or hospice) care (12,16).

4. Long-term CV monitoring and management in cancer survivors

Long-term CV risk in cancer survivors

Cancer survivors who have been exposed to cardiotoxic cancer therapies without developing overt cardiac dysfunction are considered to be in stage A HF. As the overall survival of patients with cancer continues to rise, more cancer survivors are faced with the risk of developing treatment-related cardiotoxicities. Cardiac disease has been found to be the leading cause of treatment-related nonneoplastic death among survivors of childhood cancer (25), breast cancer (26), and Hodgkin lymphoma (27). In a community-based, retrospective cohort study of 36,236 adult-onset cancer survivors (28), an increased risk of heart disease was found in patients diagnosed with breast, lung/bronchus, multiple myeloma, and non-Hodgkin lymphoma, when compared with non-cancer controls. Moreover, cancer survivors who developed CV disease had significantly worse all-cause mortality when compared with cancer survivors without CV disease (28). The increased CV risk may be driven by the shared risk factors for cancer and CV disease, the direct impact of cancer

therapy on the heart, an existing care gap in the cardiac care of patients with cancer and the increasing population of adult cancer survivors. It is important to take strategies to improve cardiovascular health in at-risk survivors long after completion of cancer therapy.

Shared risk factors in cancer and CV disease

Cancer and CV disease have similar risk factors, such as tobacco smoking, obesity, and diabetes mellitus (3). This may suggest shared biological mechanisms exist. Chronic systemic low-grade inflammation and oxidative stress are possibly involved in such mechanisms (3). These conditions increase the risk of coronary artery disease, cardiomyopathy, and cardiac sudden death in cancer survivors. In a relatively young survivor population in which modifiable cardiovascular risk factors were assessed, researchers observed that the presence of hypertension in particular increased the risk for severe cardiac events in a manner that was independent of the cancer therapy-related risk (29). This finding reinforces the need for careful screening of adult survivors for early detection of CV risk factors, and appropriate management may improve the cardiac outcome in cancer survivors.

Long-term risk of chemotherapy-induced cardiotoxicity

Most cardiotoxicity after anthracycline-containing therapy occurs within the first year (6). However, late-onset (>10 years) anthracycline-induced cardiotoxicity can potentially occur (30). Periodic screening with cardiac imaging and biomarkers, such as BNP, should be considered in survivors, particularly in those treated with high cumulative doses or who demonstrated reversible LV dysfunction during cancer treatment (11). Early discontinuation of cardioprotective HF therapy is not recommended (11). Anthracycline-related cardiotoxicity (cardiotoxicity type 1) is generally considered to be irreversible, while type 2 cardiotoxicity related to trastuzumab is frequently reversible. Cessation of HF treatment after normalization

of LVEF may be considered in patients with trastuzumab-induced cardiotoxicity (11).

5. Conclusions

Cardiac dysfunction developing during or after the completion of cancer therapy is a growing heath concern that should be addressed in a multidisciplinary setting. Many questions remain unanswered: how can we predict the development of cardiotoxicity, what is the best prevention strategy, how should we monitor those at risk of cardiac dysfunction, what are the best treatment strategies, and how long should HF treatment be continued in patients with stage B HF. There is an urgent need for collaborative research to address these questions.

Conflict of Interest

The authors declare no conflicts of interest.

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Figure Legend

Figure 1 Overview of the continuum of cardiovascular care on a timeline of cancer management.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure