Chemotherapy induced cardiotoxicity

Predictors
And
Protectors

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Introduction

Heart disease and cancer are the two major causes of morbidity and mortality worldwide, accounting for at least 70% of the medical reasons for mortality across the globe.[1]

Cancer, once seen as a problem only of high-income countries, is now a leading global cause of death responsible for one in three premature deaths from non-communicable diseases. The global trend is set to continue over the next decades through population and lifestyle changes, part of an ongoing demographic and epidemiologic transition that will see the 14 million new cancer cases and 8 million cancer deaths estimated worldwide in 2012 rise by 55% by 2030.[2]

Advances in treatment have led to improved survival of patients with cancer, but have also increased morbidity and mortality due to treatment side effects.[3] Cardiovascular diseases (CVDs) are one of the most frequent of these side effects, and there is a growing concern that they may lead to premature morbidity and death among cancer survivors.[4] This may be the result of cardiotoxicity, which involves direct effects of the cancer treatment on heart function and structure, or may be due to accelerated development of CVD, especially in the presence of traditional cardiovascular risk factors.[5]

Furthermore, the inability to predict the long-term consequences of cancer treatment associated cardiovascular side effects leads to under- or overdiagnosis of CVD, sometimes resulting in the failure to prevent adverse events and sometimes to inappropriate interruption of a potentially lifesaving cancer treatment.[6]

According to cancer research UK statistics in 2020, 28% of all cancer patients in UK are receiving chemotherapy as palliative or curative treatment.[7]

Chemotherapy: How does it affects the heart?

Many anticancer therapies are known to have deleterious effects on the cardiovascular (CV) system (Table 1).[8]

Table 1: Examples of anticancer therapies with associated CV complications or toxicities.

Anticancer agents	Cancer use	Type of cardiotoxicity	Frequency
Anthracyclines			
Doxorubicin	Breast, sarcoma, lung, bladder, gastric, prostate, leukemia, lymphoma	HF LVD Arrhythmia	Common
Alkylating agents			
Ifosfamide	Testicular, sarcoma, lymphoma	HF LVD Myopericarditis Arrhythmia	Common
Antimetabolites			
Fluorouracil	Colon, pancreatic, breast, head and neck	Coronary vasospasm Ischemia Arrhythmia LVD Myocarditis	Common Uncommon Rare
Antimicrotubules agents			
Docetaxel	Breast, lung, prostate, gastric, head and neck	HF LVD Arrhythmia	Uncommon
Monocolonal antibodies (HER2)			
Trastuzumab	Breast, gastric, gastroesophageal	HF LVD	Common
Small molecule TKIs			
Dabrafenib	Melanoma	QT prolongation HF LVD VTE	Common Rare

HER2, human epidermal growth factor receptor 2; HF, heart failure; LVD, left ventricular dysfunction; TKI, tyrosine kinase inhibitor; VTE, venous thromboembolism.

In particular, the cardiologist should have a thorough understanding of the prognosis, intended treatment plan, estimated benefit of the proposed treatment, cardiac and relevant non-cardiac toxicities and alternative treatment options. Conversely,

oncologists and hematologists should be informed of the patient's CV risk factors and the status of pre-existing CV disease (CVD) along with their prognosis.[9]

Anthracyclines have high efficacy for treatment of solid tumors and hematological malignancies, and avoiding their use due to concerns about cardiac side effects may negatively impact prognosis.[10,11] On the other hand, anthracyclines may cause irreversible cardiac damage, which in turn affects prognosis.[12] For example, doxorubicin is associated with a 5% incidence of congestive HF when a cumulative lifetime dose of 400 mg/m2 is reached, and higher doses lead to an exponential increase in risk, up to 48% at 700 mg/m2.[13] However, there is considerable variability among patients in their susceptibility to anthracyclines. While many tolerate standard-dose anthracyclines without long-term complications, treatment-related cardiotoxicity may occur as early as after the first dose in other patients.[14] The most commonly accepted pathophysiological mechanism of anthracycline-induced cardiotoxicity is the oxidative stress hypothesis, which suggests that the generation of reactive oxygen species and lipid peroxidation of the cell membrane damage cardiomyocytes.

The cardiotoxicity of anthracyclines may be acute, early or late. Acute toxicity, predominantly supraventricular arrhythmia, transient LV dysfunction and electrocardiographic (ECG) changes, develops in <1% of patients immediately after infusion and is usually reversible. However, acute cardiac dysfunction may also reflect myocyte injury that eventually can evolve into early or late cardiotoxicity.[6]

Predictors of cardiotoxicity

The prediction of long-term cardiovascular prognosis is frequently challenging because patients with cancer typically receive multiple cancer drugs and sometimes radiation, with the potential for cardiotoxic effects from interactions among the different therapeutic modalities.[15]

Cancer patients with pre-existing CVD or CV risk factors are at a greater risk of cardiac complications from anticancer therapies.[9]

The following measures can be done to predict cardiotoxicity:

1. ***Baseline CV risk assessments (pre-anticancer therapy):***

   While CV risk factors should be controlled in all patients with cancer, a thorough CV risk factor assessment is essential before the initiation of anticancer therapies, especially those therapies with known CV toxicities (Table 2). A comprehensive evaluation with appropriate initiation of risk reduction strategies may decrease the likelihood of developing cancer-related CV complications and/or disease.[16-18]

   Table 2: Common clinical factors that may indicate a patient at higher risk for cardiovascular dysfunction during contemporary anticancer treatment.

Prior anthracycline-based therapy
Elderly (>75 years old)
Prior mediastinal or chest radiotherapy
HTN (Before or at the time of treatment)
Smoking exposure (Current or previous)
Very young (<10 years of age)
Previous combined treatment with trastuzumab and an anthracycline
Elevated cardiac biomarkers before initiation of anticancer therapy
Baseline abnormal systolic LV function with LVEF <50%
Pre-existing DM

DM, Diabetes Mellitus; HTN, Hypertension; LV; Left ventricular, LVEF, Left ventricular ejection fraction.

2. ***Baseline measurement of cardiac biomarkers:***

   Various ChT regimens are associated with a wide range of potential CV toxicities and in selected situations cardiac biomarkers may help detect or predict CV toxicities, particularly cardiomyopathy and/or heart failure (HF). The exact role and the timing of biomarker measurement in each patient undergoing potentially cardiotoxic ChT is yet to be determined. The specific timing of when to measure cardiac biomarkers in relation to ChT has varied significantly in different clinical studies. In selected high-risk patients, such as those with relapsed multiple myeloma, or those receiving high doses of

cardiotoxic ChT (particularly anthracyclines), a baseline biomarker evaluation before the initiation of ChT should be considered, as this may identify individuals at greatest risk for developing CV dysfunction.[19-23]

Troponin

The most compelling initial data relate to troponin elevations associated with anthracycline exposure. In one study of 703 cancer patients, normal troponin I levels before and after anthracycline based ChT were associated with a low incidence of cardiac events (1%) during the >3-year follow-up, while patients with elevations in troponin I during the course of ChT had a greater incidence of major adverse cardiac events.[24]

A more recent study demonstrated that absolute changes in high-sensitive (hs)-troponin levels were especially predictive of future cardiotoxicity in patients treated with anthracyclines,[25] though this study needs further validation. There is some evidence to suggest that an elevated hs troponin level at baseline may also indicate a higher risk of cardiac events.[26]

Natriuretic peptides (NPs)

The utility of natriuretic peptides (NPs) [B-type NP (BNP), N-terminal pro-BNP (NT-proBNP)] to identify those at risk for anthracycline-induced CV dysfunction is less clear,[26,27,28] but may be of value as a screen for patients at high risk.[29] In a prospective study of 95 patients with relapsed multiple myeloma who were being treated with proteasome inhibitor therapy, the baseline NP level was the most predictive clinical tool for predicting a cardiac event. Early rises in NP levels during initial therapy in this study was highly predictive of the development of a cardiac event and the detection of a cardiac event had a major negative impact on the overall survival (OS) of these patients.[23]

3. Baseline electrocardiogram:

The importance of drug induced QTc prolongation as a key drug safety parameter is widely acknowledged. The QT interval is a surrogate marker for cardiac repolarization abnormalities, with significant prolongation associated with the development of potentially life-threatening ventricular arrhythmias such as torsade de pointes.[30] While QT interval prolongation is common in

cancer patients, clinical events are rare,[31] but may be lethal. The QTc interval should be calculated by either of the two most standardized formulas, Bazett's QT/(RR1/2) or Fridericia's QT/ (RR1/3), and the comparative measurements during treatment should all utilize the same chosen method. Fridericia's formula may be preferable in the cancer population as there is less over- and under-correction in patients with tachycardia or bradycardia, respectively.[32-34]

4. ***Baseline evaluation of left ventricular ejection fraction:***

Currently, therapies associated with a significant risk of HF or left ventricular (LV) dysfunction (LVD) include, but are not limited to, anthracyclines, human epidermal growth factor receptor 2 (HER2) molecular-targeted therapies (such as trastuzumab or pertuzumab), vascular endothelial growth factor (VEGF) signaling pathway inhibitors (such as sunitinib, sorafenib and bevacizumab) and some proteasome inhibitors (carfilzomib). Quantitative evaluation of LV ejection fraction (LVEF) and diastolic function before the initiation of potentially cardiotoxic ChT can help to identify individuals at higher risk of future CV complications and to establish a baseline, should symptoms suggestive of CV dysfunction occur during treatment. This approach is supported by multiple governing organizations including the American Society of Clinical Oncology (ASCO), the American Society of Echocardiography (ASE), the European Association of Cardiovascular Imaging (EACVI) and the ESC.[35-37] Moreover, the assessment of LV function before the initiation of therapy is recommended by the United States Food and Drug Administration (FDA) for certain therapeutics including trastuzumab and pertuzumab. For patients monitored with global longitudinal strain (GLS) evaluations, a baseline assessment is also essential for comparison.[35]

Protectors from cardiotoxicity:

Patients receiving anticancer therapies known to be associated with cardiotoxicity should be considered as stage A HF patients (at risk of HF but without structural heart disease or symptoms of HF).[38]

1. *Prevention with CV therapeutics:*

In patients with preexisting CVD who are receiving potentially cardiotoxic therapy (doxorubicin, trastuzumab or both), there is often a measurable change in LVEF over the span of 3 years, and this is not limited to higher CV risk patients. Patients treated with these therapies are at higher risk for the development of subsequent HF and therapy directed at prevention of the progression of LVD is warranted. There are a small number of studies to suggest that angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs) or selected beta blockers (BBs) such as carvedilol and nebivolol may be the preferred agents to reduce the risk of cardiotoxicity (Table 3).[39,40]

Table 3: Classes of cardiovascular therapeutics that have some clinical trial evidence to suggest cardioprotection during anticancer therapy.[a]

Class of CV therapy	Examples
ACE-I	Enalapril
ARB	Candesartan
MRA	Spironolactone
Statins	Pravastatin (many statins) Atorvastatin
Iron chelation/topoisomerase II inhibitor	Dexrazoxane
Antiplatelet	Aspirin
Anticoagulant	Enoxaparin Rivaroxaban/apixaban
BB	Carvedilol Nebivolol
Combination of ACE-I/BB	Enalapril Carvedilol

ACE-I, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BB. Beta blocker; CV, Cardiovascular; MRA, Mineralocorticoid receptor antagonist.

[a] Cardioprotection: any evidence that indicates the medication attenuates any CV dysfunction that may occur with potential cardiotoxic anticancer therapy.

In a single-centre trial in Spain of 90 subjects with certain hematological malignancies, patients randomly assigned to receive enalapril and carvedilol

showed a significant reduction in a combined end point of death, HF or final LVEF < 45% at 6 months compared with placebo.[41] In another single-centre trial in Norway (n =130), patients undergoing anthracycline-based therapy, with or without trastuzumab and radiation, were independently randomly assigned to receive candesartan, metoprolol succinate or matching placebo(s) in a 2 2 factorial design.[42] Candesartan, but not metoprolol, was associated with preservation of LVEF. It is notable that the study population did not have a high percentage of comorbid conditions or cardiac risk factors, and the absolute rate of cardiotoxicity was low. A third study of breast cancer patients receiving HER2 antagonists (n = 94) randomized patients to perindopril, bisoprolol or placebo.[43] Preservation of LVEF was observed with both perindopril and bisoprolol; however, there was no statistical difference in the prevention from LV remodeling (measured by changes in LV volume), the primary end point of the study. More recently, a randomized, placebo-controlled trial of 200 breast cancer patients initiated on anthracycline therapy found no difference in LVEF at 6 months with carvedilol but did show improvement in diastolic function and protection from troponin elevations.[44] The study was limited to 6-month follow-up. Another study of patients with HER2-positive breast cancer demonstrated that trastuzumab-induced cardiotoxicity was more frequent in patients with prior exposure to anthracyclines compared with those without anthracycline exposure (38% versus 25%, P = 0.002). Both lisinopril and carvedilol were effective in preventing cardiotoxicity in patients receiving trastuzumab with prior exposure to anthracycline.[45] In a separate therapeutic class, the aldosterone antagonist spironolactone has also been studied in a single trial of 83 breast cancer patients on anthracyclines, with improvement in LVEF compared with placebo.[46] These studies offer evidence of modest clinical benefit, but overall results are a mixed reflection of different study populations including many low-risk patients, different anticancer therapies and clinical trial end points. Further studies are needed to delineate the optimal patient selection and therapeutic regimen for effective toxicity prevention, focusing on patients at highest risk for developing cardiotoxicity based on the ChT regimen prescribed and known CV risk factors (Table 2).

Dexrazoxane is primarily an iron chelator and may reduce the production of free radicals formed at the time of anthracycline therapy. It also modifies topoisomerase II to prevent its binding with anthracycline. This therapy has been established to be effective in children and is approved in metastatic

breast cancer when the total doxorubicin dose (or equivalent) is >300 mg/m2 .[47-49] However, this strategy does not address the challenge faced by patients with pre-existing cardiomyopathy when they require anthracyclines. In a small number of such patients, concomitant administration of dexrazoxane from the beginning of anthracycline therapy, regardless of the type of cancer, was shown to be effective and permitted successful delivery of anthracycline-based ChT without cardiac decompensation.[50] Although larger prospective trials are warranted to examine the use of dexrazoxane as a cardioprotectant in patients with pre-existing cardiomyopathy who require anthracyclines, it is a reasonable strategy in the meantime for patients who do not have an effective alternative therapy.

2. ***Treatment of hyperlipidemia during anticancer therapy:***

There is recent evidence that hyperlipidemia has a contributory effect to inflammation in patients with cancer.[51] A propensity-matched, cohort study (n= 201) found benefit to continuous statin treatment (compared with no or non-continuous treatment) in patients with breast cancer treated with anthracyclines.[52] A small randomized study (n= 40) suggested a benefit to statins as a cardioprotective therapy as well, though it did not reach its primary end point.[53]

3. ***During cancer treatment: cardiac safety surveillance:***

Non-radiating imaging

Accurate, reproducible, quantitative volumetric analyses are preferred. Three-dimensional (3D) echocardiography, CV magnetic resonance (CMR) imaging and multi-gated acquisition (MUGA) scanning provide quantitative volumetric analysis with superior accuracy and serial reproducibility compared with two-dimensional (2D) echocardiography, predominantly due to direct volume measurement without geometric assumptions.[54-57] Non-ionizing radiation modalities may be most appropriate due to concerns regarding cumulative radiation dose in cancer patients,[58] as traditional MUGA scanning can expose patients to significant radiation with each exam.[59] It is also recognized that echocardiography provides substantial additional information on cardiac structure, valve function, hemodynamics and physiology not typically found with MUGA scanning. The use of CMR

imaging is increasing, but limitations in availability, cost and expertise may impede a wide adoption of this technique.[35] Quantitative 2D echocardiography using Simpson's biplane method is the most appropriate method when 3D echocardiography and CMR imaging are not routinely available; echocardiographic contrast agents are helpful when endocardial definition is inadequate with routine imaging.[60] The most appropriate modality will vary with patient characteristics as well as centre availability and local expertise.

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