

Assessing and monitoring cardiac function in cancer patients

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Abstract

The use of chemotherapy is associated with improved survival rates for patients with neoplastic disease. Cardiac toxicity is a feature of several therapeutic agents (e.g., anthracyclines) and patients require careful monitoring during treatment. The adverse effects of chemo- and radiotherapy may not be apparent for some time post completion of treatment and patients may require long-term follow-up by oncologists and cardiologists. In this invited article we review the therapies associated with significant cardiac toxicity and provide guidance on the assessment of patients during chemotherapy and during chronic surveillance.

Keywords: cancer, chemotherapy, heart failure, cardiotoxicity

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Introduction

Progress made in screening and therapies have greatly reduced morbidity and mortality due to cancer over the past few decades. In 2006, there were 1.13 million cancer survivors in the United Kingdom who were up to 10 years from diagnosis [1]. Some of these therapies do however carry a significant risk of cardiotoxicity and after-cancer recurrence; cardiac events are the most common cause of death in these patients. While coronary ischemia, arrhythmia, thromboembolism, and QT prolongation have all been noted as acute complications of specific chemotherapies (Table 1) [2], in this review we focus on cardiomyopathy due to cancer therapy.

The mechanisms of left ventricular (LV) dysfunction have been extensively studied, yet few prospective clinical studies exist and there is a lack of consensus and guidelines regarding best practice in terms of assessing, monitoring, and managing these patients. The risk-benefit calculations are therefore challenging for the oncologists and cardiologists involved in their care.

Chemotherapy agents

Anthracyclines (doxorubicin, epirubicin, idarubicin)

Anthracyclines are recognized as highly efficacious and are still one of the most commonly used chemotherapies in treating adult solid organ and hematological tumors. They are also renowned for causing a dose-dependent and progressive toxic cardiomyopathy [3].

Therapy	LV dysfunction	Ischemia	Prolonged QT	Arrhythmia
Anthracyclines Doxorubicin, epirubicin, idarubicin	>5% incidence			
Alkylating agents Cyclophosphamide, ifosfamide	>5% incidence			
Humanized monoclonal antibodies Trastuzumab, bevacizumab	>5% incidence	<2% incidence		
Small molecule tyrosine kinase inhibitors Sunitinib, dasatinib, lapatinib	2-5% incidence		>5% incidence	
Erlotinib, sorafenib		2-5% incidence	>5% incidence	
Radiotherapy	>5% incidence			
Antimetabolites 5Fluorouracil, capecitabine		>5% incidence		
Antimitotubule Paclitaxel		2-5% incidence		>5% incidence
Proteasome Inhibitors Bortezomib	2-5% incidence			

Table 1 Incidence of cardiac complications of commonly used chemotherapies. A summary of the major chemotherapeutic classes and their estimated incidence of cardiac complication based on meta-analysis (modified from Yeh and Bickford [2]).

There are three distinct types of cardiotoxicity associated with anthracyclines:

- Acutely (<1%) or subacutely, they can cause a pericarditis-myocarditis syndrome, or acute left ventricular failure (usually reversible).
- A chronic, progressive cardiomyopathy can present within the first year following the start of treatment.
- Late-onset cardiomyopathy can manifest years to decades after anthracycline treatment. In the pediatric population, the effects are often not seen until up to 25 years post-chemotherapy.

We know from a large experience of endomyocardial biopsies that anthracyclines destroy myocytes. There have been considerable efforts into finding ways to identify those at risk and protect the myocardium from anthracyclines. Identified “risk factors” are: underlying cardiovascular disease, pregnancy, hypertension, pre-existing cardiac disease, age >65 or <18 at time of therapy initiation, combination chemotherapy, radiation therapy, intravenous bolus administration, high cumulative dose [4, 5]. Retrospective analyses suggest that doxorubicin cardiotoxicity occurs at dosages considerably lower than first appreciated: the cumulative dosage that correlated with a 5% incidence of heart failure ranged between 400 and 450 mg/m² [6].

Attempts to minimize the cardiotoxicity of anthracyclines include dose limitation, schedule modification,

use of less cardiotoxic analogues, and use of cardioprotective agents. There has been some evidence that adding dexrazoxane (a free radical scavenger) can be cardioprotective [7]. There are, however, concerns that it may interfere with the antitumor effect of the anthracyclines and the American Society of Clinical Oncology currently advises against its routine use [8].

Alkylating agents (cyclophosphamide, ifosfamide)

Acutely, cyclophosphamide has been associated with a hemorrhagic myocarditis. It has also been associated with heart failure in up to 28% of patients. Cardiotoxicity has been shown to be dose related, irreversible and typically manifests within 2 weeks of therapy [9]. Risk factors for cardiotoxicity include previous anthracycline use and previous radiotherapy.

Humanized monoclonal antibody based tyrosine kinase inhibitors (bevacizumab, trastuzumab)

Cancer patients receiving trastuzumab (Herceptin®) are a relatively new population (it was first approved by the United States Food and Drug Administration in 1998). It is indicated in combination with paclitaxel for first-line treatment and as a single agent for second- or third-line treatment of metastatic breast cancer. Approximately 25% of women with breast cancer will have a tumor overexpressing human epidermal growth factor 2 (HER2) and addition of trastuzumab to adjuvant

therapy has been shown to reduce their risk of recurrence at 3 years by half and improve survival by approximately a third [10]. It has also recently been approved for use in HER2-positive metastatic stomach cancer.

The pivotal trials of trastuzumab observed an unexpected risk of cardiac dysfunction. Patients with breast cancer are commonly treated with both trastuzumab and an anthracycline, which poses the problem of isolating effects of either agent from a potential synergistic interaction. Cardiotoxicity has however been shown to be rare in patients on trastuzumab alone.

Endomyocardial biopsy specimens evaluated post-trastuzumab exposure have not shown any changes that suggest significant myocyte destruction [11]. HER2 receptors exist in the heart and it is thought the HER2/erbB2 system may modulate the effects of oxidative stress in the cardiac myocyte. Some postulate that these drugs interfere with myocyte metabolism and, in the patient with impaired contractile reserve due to previous or concomitant anthracycline or alkylating agents, this may manifest as deterioration in cardiac function.

Unlike anthracyclines trastuzumab rarely causes death, is not cumulatively dose related, and the majority of patients who developed trastuzumab-related congestive heart failure and discontinued trastuzumab had recovery of left ventricular ejection fraction (LVEF) with subsequent follow-up [12]. The long-term effects of these drugs remain to be seen.

Small molecule tyrosine kinase inhibitors (lapatinib, imatinib, sumatanib)

The cardiac safety of lapatinib was recently evaluated in the 3,689 patients enrolled in phase I to III lapatinib clinical trials. Of these patients, 1.6% experienced a cardiac event. In patients treated with prior anthracyclines, trastuzumab, or neither, the incidence of cardiac events was 2.2%, 1.7%, and 1.5%, respectively. The mean time to onset of cardiac events was 13 weeks [13].

Radiotherapy

Mediastinal radiation potentially leads to inflammation and progressive fibrosis of all of the heart structures. It is known to cause pericardial disease, accelerated coronary artery disease and has been implicated in conduction disease although causality is difficult to establish. In comparison to the systolic dysfunction seen with chemotherapy these patients have been shown to develop a restrictive cardiomyopathy. The

occurrence and manifestation of radiation-related cardiac disease depends mostly on radiation dose, volume of the heart exposed, and specific radiation delivery techniques used. A study of 4,122 patients found the relative risk of cardiac death was 12.5 at radiation doses of 5-15 Gy, and 25.1 at >15 Gy [14]. The Oxford meta-analysis of randomized trials also demonstrated an increased risk of ischemic heart disease [15], however the majority of the patients included in these studies would have been exposed to large volumes of radiotherapy and modern radiation therapy techniques (used since the mid 1980s) with three-dimensional planning, computed tomography guided therapy and lower radiation doses seem to have significantly reduced this risk [16].

Defining and detecting cardiac dysfunction

In order to assess and monitor these patients we have to identify how we recognize and define "cardiac dysfunction". When the pivotal trials of trastuzumab established that there was associated cardiotoxicity [17], a cardiac review committee established the following criteria to identify cardiac dysfunction:

- (1) A decrease in cardiac LVEF that was either global or more severe in the septum.
- (2) Symptoms of congestive heart failure.
- (3) Associated signs of heart failure.
- (4) Decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of congestive heart failure, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms.

Initial assessment

Currently in most institutions it is the oncologists who are assessing these patients. Ideally prior to antineoplastic therapy, they will conduct a detailed baseline assessment of functional capacity, known cardiac history as well as risk factors. Notably many of the symptoms of cancer can be difficult to distinguish from cardiac symptoms (chest pain, breathlessness, leg swelling). Oncologists should identify patients at particular risk of cardiotoxicity so that the choice of therapy and risk factors may be optimized and they can be monitored more vigilantly.

Prior to starting therapy, one needs a baseline ECG and study of cardiac function. The most common non-invasive method of monitoring myocardial toxicity has been the assessment of LV systolic function, with either

radionuclide ventriculography or echocardiography. The two measurements are not interchangeable; the same technique should be used for serial measurements. Where possible, this should also include the same operator, machine, and calculation algorithm.

After baseline assessment, patients with LV dysfunction or modifiable cardiac risk factors should be referred for cardiology review. There is some trial evidence for the efficacy of ACE inhibitors in preventing the decrease in LVEF observed in patients after high-dose chemotherapy [18]. The regime of chemotherapy might be modified accordingly.

In the United Kingdom, the National Institute for Health and Clinical Excellence recommends cardiac functional assessments should be repeated every 3 months during trastuzumab treatment. If the LVEF drops by 10% or more from baseline and to below 50%, trastuzumab treatment should be suspended. A decision to resume trastuzumab therapy should be based on a further cardiac assessment and a fully informed discussion of the risks and benefits between the individual patient and his or her clinician [19]. There are consensus guidelines for anthracyclines that adhere to a similar protocol, however they advocate long-term follow-up on a yearly or two-yearly basis depending on the cumulative dose of chemotherapy given and the risk profile of the patient.

Methods of monitoring

MUGA

Radionuclide ventriculography or multiple gated acquisition scan (MUGA) is frequently used. In its favor, it is less subject to observer variability [20] than echocardiography, however it does involve exposure to radiation, is associated with higher cost and does not give us any information other than ejection fraction in comparison to echocardiography, which may identify pericardial or valvular disease as well. Choice between echocardiography and MUGA is based on provider preference or regional practice.

Echocardiography

Echocardiography is widely available and relatively inexpensive and hence is often the initial investigation of choice for evaluating systolic function. While disputed by some, ejection fraction is currently the standard method of screening for cardiotoxicity.

Poor quality echo images due to surgery and inter-observer variability may confound these measurements. Contrast or 3D echocardiography might improve reproducibility, and the laboratories performing such studies should have evidence that they can reliably and reproducibly identify a 10% change in EF as a true change [21].

Many studies have aimed to identify more sensitive indicators of early cardiotoxicity, including Tei Index, tissue Doppler, and myocardial strain [22, 23]. Several have suggested that diastolic dysfunction is an early sign of anthracycline-induced cardiac dysfunction. These are generally small studies and further validation is necessary [24–26].

Other methods currently being evaluated

While most of the methods currently used do monitor for deterioration in systolic dysfunction, there is an argument that cardiac dysfunction is not best appreciated by measurements of systolic function. It may be preceded by asymptomatic or sub clinical cardiac dysfunction undetectable at bedside evaluation and/or defined by abnormalities measured by standard non-invasive imaging techniques

Dobutamine stress echo

It is known that patients with mild and sub-clinical deterioration of systolic LV function can compensate for a decreased cardiac output with a number of adaptive mechanisms, i.e., increasing preload, heart rate, and contractility during stress. Dobutamine stress echo is an established method of assessing contractile reserve in ischemic and valvular heart disease. It is a generally well-tolerated test, which can be repeated. It does however require a less widely available skill set and its role in assessing patients on chemotherapy is less well established [27]. No studies have evaluated the benefits of non-invasive evaluation of asymptomatic cancer survivors for cardiac dysfunction. Yeung et al tested 29 children, 19 of whom had received anthracyclines up to 6 years earlier, with exercise echocardiography. They found an average increase in fractional shortening of 3% in the anthracycline group compared with an average increase of 23% in the control group, although fractional shortening at rest was normal in all participants [28]. This raises the question of how we would interpret and act on such findings.

CMR

Cardiac magnetic resonance imaging (CMR) has the benefits of low intra/inter-observer variability and high test-retest reproducibility. It also has the ability to detect early myocardial damage. Wassmuth et al have demonstrated that CMR may be useful at detecting the sub-clinical effects of chemotherapy. Increased contrast enhancement on day 3 predicted significant decline at 28 days [29]. It could be useful in patients with poor echo pictures and in fact as more CMR services become available, it may serve as a simple non-invasive tool in following up patients post chemotherapy.

Biomarkers

It is well recognized that cardiac dysfunction may become evident weeks, months or years after high-dose chemotherapy. The possibility of developing an early marker of myocardial injury would allow us to appropriately monitor those at higher risk. Troponin and BNP have both been explored in detecting cardiac damage and risk stratifying patients. Cardinale et al demonstrated that troponin I is a sensitive and specific marker for predicting the development and severity of ventricular dysfunction. In one study of 703 patients, elevation of troponin I levels 0–72 hours after chemotherapy administration and at 1 month, predicted a late decline in LVEF and a composite of cardiac events [30]. Cardinale also demonstrated a strong relationship was also found between NT-proBNP value at 72 hours, and LVEF changes at 12 months. While these initial studies of biomarkers as a screening tool are promising the numbers are small and more work in this area is needed for further validation.

Conclusion

Patients with cancer have a substantial risk of developing heart disease as a result of chemo- and radiation therapy. Cardiotoxicity, not only negatively affects the cardiac outcome of patients with cancer, but also largely reduces the range of suitable therapies. The optimal interval and duration as well the cost effectiveness of cardiac monitoring remain undefined. That being said, from the evidence and consensus guidelines we do have it is possible to design sensible monitoring protocols. These need to be clearly defined and regular quality assurance is key. The process of assessing and following up these patients needs to be systematic not only to avoid missing pathology, but also

for future research purposes. Most importantly where cardiac dysfunction is identified, there needs to be a clear avenue for communication and collaboration between oncologists and cardiologists within a multi-disciplinary cancer team. •

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