Cardio-oncology

Cardio-oncology is the care of cancer patients with cardiovascular disease. While it has been established as a speciality for a few years in the USA and in some parts of Europe, it is in its infancy in the UK. However, the speciality is rapidly expanding in the UK with a number of hospitals developing cardio-oncology services. This review gives the reader an overview of this exciting new specialty.

What is cardio-oncology?

Cardio-oncology is the prevention and management of heart disease in cancer patients (Yeh and Bickford, 2009). While the bulk of work is related to cardiovascular toxicity of cancer therapies, there are other interactions between cancer and heart disease with many common risk factors and disease pathways at cell and molecular level (Suter and Ewer, 2013).

The mortality rate among patients with cancer has decreased dramatically over the last 20–30 years. However, the toxicity of conventional cancer treatment (both chemotherapy and radiotherapy) is greater than previously appreciated and is a leading cause of morbidity and mortality in survivors (Barac et al, 2015). New 'targeted therapies' are being rapidly developed, many of which have recognized or unrecognized cardiovascular toxicities. The cardiac toxicities of cancer treatment include heart failure, cardiac ischaemia, arrhythmias, pericarditis, valve disease, and fibrosis of the pericardium and myocardium (Lenihan and Cardinale, 2012) (*Figure 1*).

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Chemotherapeutic agents can broadly be divided into cytotoxic agents (anthracyclines, e.g. doxorubicin, taxanes, e.g. paclitaxel and others like 5-fluorouracil, cyclophosphamide and cisplatin) and molecular targeted therapy (monoclonal antibodies, e.g. trastuzumab, tyrosine kinase inhibitors, e.g. sunitinib, and vascular endothelial growth factor antibodies, e.g. bevacizumab) (*Table 1*). The cardiovascular side effects of these agents are varied (*Table 2*) and have traditionally been divided into type 1 and type 2 effects although there may be some overlap (Plana et al, 2014).

Type 1 effects are commonly caused by anthracyclines and result in myofibrillar disarray causing cumulative and dose-related damage. These effects appear to be permanent and irreversible. Type 2 effects are caused by trastuzumab, are not dose related, show no ultra-structural abnormalities and the cardiac effects are thought to be reversible. However, there is growing evidence that this demarcation into type 1 and 2 effects may be somewhat arbitrary, as there is considerable overlap (Bloom et al, 2016).

Figure 1. Cardiovascular side effects of cancer treatment.

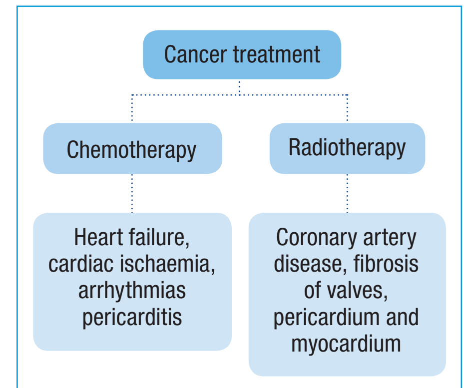

Table 1. Mechanisms of action and uses of common cardiotoxic chemotherapeutic agents

Cytotoxic agents	Anthracyclines – doxorubicin, daunorubicin, epirubicin	Intercalate into nuclear DNA, impair topoisomerase II, cell transcription and division, producing reactive oxygen species	Leukaemia and soft tissue tumours
	Taxanes – paclitaxel, docetaxel	Polymerise tubulin leading to dysfunctional microtubules disturbing cell division	Breast and ovarian cancer
	Other agents – 5-fluorouracil, capecitabine, cyclophosphamide, cisplatin	Bind to DNA causing crosslinking and ultimately apoptosis	Testicular, bladder, ovarian cancer
Molecular-targeted therapy	Human epidermal growth factor 2 receptor (HER2) antibody – trastuzumab	Humanized immunoglobulin G1 monoclonal Ab directed against the HER2 protein	Breast cancer
	Tyrosine kinase inhibitors – lapatinib, sunitinib, imatinib	Stop protein activation by blocking signal transduction cascades	Breast, gastrointestinal stromal, renal cancer, leukaemia, non-Hodgkin's lymphoma
	Vascular endothelial growth factor (VEGF) inhibitors – bevacizumab, sorafenib, axitinib	Inhibit tumour-associated angiogenesis mediated by VEGF and VEGF receptors	Brain, kidney, lung, colon cancer
	Other biologic agents – rituximab	Monoclonal antibody acting against CD20 protein	Leukaemia, lymphoma

Table 2. Cardiovascular side effects of chemotherapeutic agents

Cardiomyopathy	Anthracyclines, vascular endothelial growth factor inhibitors, trastuzumab
Coronary spasm and ischaemia	Fluoropyrimidines
Diabetes and metabolic syndrome	Antiandrogen therapy
Hypertension	Vascular endothelial growth factor inhibitors
Arrhythmias	Dasatinib, nilotinib, paclitaxel
Venous and arterial thromboembolism	Vascular endothelial growth factor inhibitors

Radiotherapy can cause cardiac damage through macrovascular and microvascular injury. The risk of radiation-induced heart disease is increased with anterior or left chest irradiation, lack of shielding, higher doses and with concomitant anthracycline chemotherapy (Lancellotti et al, 2013). Patients who received radiotherapy historically are at increased risk compared to current radiotherapy regimens because of the development of better shielding protection.

Presentation

Cardio-oncology patients can present in a number of ways (Bellinger et al, 2015). Depending on the cardiac diagnosis (e.g. heart failure *vs* ischaemia) different investigations and management plans are formulated.

Investigations

Imaging

Cardiac imaging is the primary investigative modality. With the known effect of chemotherapy on cardiac function, cardiac imaging has been used to monitor this. Echocardiography is the key initial imaging investigation. It is widely available, inexpensive and does not expose the patient to radiation. It can also evaluate systolic and diastolic function in addition to valve disease and pericardial effusions. Echocardiography has been used primarily for surveillance of those undergoing cardiotoxic treatment. Older guidelines focussed on repeated monitoring of ejection fraction with a decrease in ejection fraction below a certain level postponing or stopping cancer treatment (Curigliano et al, 2012). Changes in ejection fraction are late markers in the assessment of cardiac function.

Ejection fraction is a composite marker reflecting longitudinal, radial and circumferential myocardial contractility. A deterioration in any one of these types of contractility can be compensated for by increased contractility in the other two directions. As such the ejection fraction may remain unchanged despite deterioration in one type of contractility and is thus an insensitive marker of myocardial function in this situation (Abraham et al, 2007). The use of three-dimensional echocardiography to obtain volumetric ejection fraction calculations is more reproducible, compares favourably with cardiac magnetic resonance ejection fraction calculations and is the preferred echocardiographic method of calculating ejection fraction (Plana et al, 2014).

Newer parameters of deformation and contractility hold the prospect of being able to identify cardiac involvement before ejection fraction changes, and thus alert clinicians early, before irreversible damage occurs. Candidate parameters include echocardiographic strain imaging, tissue Doppler annular velocities and chamber volumes. Current guidelines recommend strain imaging in monitoring for cardiotoxicity (Lancellotti et al, 2013).

Other imaging modalities also have a role. Cardiac magnetic resonance imaging can complement echocardiography by demonstrating the location of focal myocardial fibrosis by late gadolinium imaging and diffuse fibrosis by the newer T1 and T2 mapping techniques (Neilan et al, 2013). Cardiac magnetic resonance can also identify acute inflammatory changes associated with chemotherapy and can be invaluable in monitoring for the resolution of cardiac oedema in this context (Thavendiranathan et al, 2013). However, cardiac magnetic resonance is limited by availability, cost and patient acceptance, making it unlikely to wholly supplant echocardiography.

Computed tomography of the coronary arteries is also a useful investigation especially when assessing the effects of radiotherapy-induced fibrosis and coronary atherosclerosis and has been recommended in European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines (Lancellotti et al, 2013; Plana et al, 2014).

Blood tests

Troponin and brain natriuretic peptide levels can be measured during chemotherapy and in case of decompensation. Elevated levels indicate some degree of myocardial cell damage and/or myocardial strain and are prognostic (Cardinale et al, 2004). However, prospective studies have not yet been undertaken to determine if initiating cardioprotective treatment in response to abnormal blood tests has a prognostic benefit.

Management and prevention

Patients with chemotherapy- or radiotherapy-induced heart failure, valve disease or coronary ischaemia should be treated as per standard European and national guidelines, but some registries suggest that cancer survivors may be undertreated for conventional cardiovascular risk factors (Meacham et al, 2010; Weaver et al, 2013). Treatment of coronary disease with stents (and associated antiplatelet agents) may be difficult if cancer surgery or treatment with chemotherapy that may seriously diminish platelet numbers, is imminent. Currently clinicians deal with these situations on an individual basis, although with national and international registries becoming available, it is hoped that these important aspects of clinical care may become standardized.

There are limited data on the cardioprotective effect of angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers and beta blockers in patients undergoing chemotherapy (Cardinale et al, 2006; Seicean et al, 2013). Their use in this context (e.g. when the ejection fraction or strain values drop significantly with chemotherapy but still remain in the 'normal' range) is unlicensed. The Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research (MANTICORE) and Prevention of Cardiac Dysfunction during an Adjuvant Breast Cancer Therapy (PRADA) trials (Pituskin et al, 2011; Heck et al, 2012) are investigating this and whether cancer therapy-related cardiotoxicity can be prevented.

Desraxozane (an iron chelator) reduces doxorubicin-induced cardiotoxicity (Cvetković and Scott, 2005). It may be initiated at the first dose of anthracycline or after a cumulative doxorubicin dosage of ≥300 mg/m^2. However, its use is licensed in the treatment of only a few cancers. Its use is not widespread and although a worsening in

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KEY POINTS

- Cardio-oncology is a new and exciting specialty involved with the prevention and management of heart disease in cancer patients.
- Chemotherapy, radiotherapy and cancer itself have cardiovascular effects.
- Cardiovascular complications include heart failure, valve disease, pericarditis, pericardial effusions, ischaemic heart disease and arrhythmias.
- Imaging is key for detecting abnormalities and monitoring patients, with the main imaging modality being echocardiography.
- Limited evidence showing the cardioprotective effect of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and beta blockers – new trials are ongoing.
- Cardio-oncology services and training opportunities are expanding in the UK.

cancer outcomes was suggested, subsequent studies have not confirmed this potential (Swain et al, 1997).

Further work has been done on the cardioprotective effect of mineralocorticoid receptor antagonists (Akolkar et al, 2015) and on statins (Seicean et al, 2012), but randomized controlled trials are awaited for both drug classes before incorporation into guidelines.

The current UK perspective – services and training

There is increased recognition that optimal cardiovascular care for cancer patients can be best delivered through dedicated cardio-oncology services. Cardio-oncology services are now being developed at a number of hospitals in the UK. Both authors are involved in establishing cardio-oncology services at their respective hospitals. Given the increased success of oncological treatments the number of cancer patients with cardiovascular problems will increase with time resulting in a greater need for cardio-oncology services.

Training programmes in cardio-oncology are well established in the USA with trainees from both cardiology and oncology undertaking these fellowships. The ultimate aim is to develop cardio-oncology services with cardiologists and oncologists working together as a team (Okwuosa and Barac, 2015). Currently only a few hospitals in the UK offer cardio-oncology fellowships. The British Cardio-Oncology Society (http://bcos.org/) aims to expand training in cardio-oncology and ultimately develop formal training programmes. **BJHM**

Conflict of interest: Both authors are members of the British Cardio-Oncology Society.

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