Cardio-Oncology

– *establishing itself as a new subspecialty in cardiology*

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Cardio-Oncology is the care of cancer patients with cardiovascular disease[1]. While it has been established a speciality for a few years in the USA and in some parts of Europe, it is now rapidly developing in the UK. This review aims to give the reader of an overview of the exciting new specialty of Cardio-Oncology.

What is Cardio-Oncology?

Cardio-Oncology is the prevention and management of heart disease in cancer patients[2]. While the bulk of work is related to cardiovascular toxicity of cancer therapies it is important to remember that there are other interactions between cancer and heart disease with many common risk factors and disease pathways at cell and molecular level[3].

The mortality rate among patients with cancer has decreased dramatically over the last 20 to 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. New "targeted therapies" are being developed at a rapid pace many of which have recognised or unrecognised cardiovascular toxicities. The cardiac toxicities of cancer treatment include heart failure, cardiac ischaemia, arrhythmias, pericarditis, valve disease and fibrosis of the pericardium and myocardium4 (Figure 1).

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 (Herceptin), tyrosine kinase inhibitors e.g. Sunitinib and Vascular endothelial growth factor antibodies (VEGFs) e.g. Bevacizumab] (Table 1). The cardiovascular side-effects of these agents are varied (Figure 2). Newer immunotherapies like Chimeric Antigen Receptor T Cell (CART) therapy have their associated cardiotoxicities5.

Radiotherapy can cause cardiac damage through macrovascular and microvascular injury (Figure 3). The risk of radiation-induced heart disease is increased with anterior or left chest irradiation, lack of shielding, higher doses and with concomitant anthracycline chemotherapy6. Patients who received radiotherapy historically are at increased risk compared to current radiotherapy regimes due to the development of better shielding protection.

Presentation

Cardio-Oncology patients can present in a number of ways. Depending on the cardiac diagnosis (e.g. heart failure versus ischaemia) different investigations and management plans are formulated.

The key role of 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. Traditionally in the USA nuclear medicine (MUGA – multi-gated acquisition)

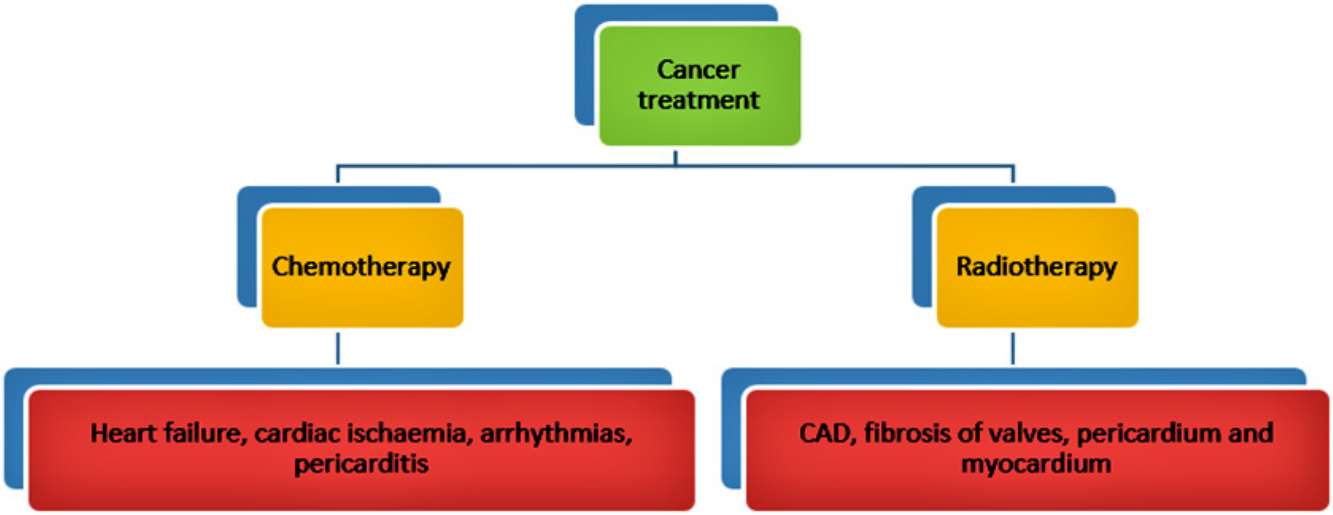


Figure 1. Cardiovascular side effect of cancer treatment

scans have been used to monitor ejection fraction (EF) in cancer patients. The predominance of this imaging technique in the USA is due to widespread availability and good reproducibility. However, such an approach has considerable drawbacks – namely repeated exposure to radiation with repeated surveillance scans and an inability to offer a more nuanced assessment of cardiac function other than EF.

In most other countries, echocardiography is the key initial imaging investigation. It widely available, inexpensive and does not expose the patient to radiation. In the UK the first national guidelines in cardio-oncology were released in March 2021 focusing on the role of echocardiography in monitoring cancer patients[7].

Other imaging modalities have their role also. Cardiac magnetic resonance (CMR) imaging can complement echocardiography by demonstrating the location of focal myocardial fibrosis and inflammation. CMR is however limited by availability, cost and patient acceptance, making it unlikely to wholly supplant echocardiography[8].

Computed Tomography of the Coronary Arteries (CTCA) is also a useful investigation especially when assessing the effects of radiotherapy-induced fibrosis and coronary atherosclerosis[9].

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 CV risk factors. The treatment of coronary disease with stents (and the associated antiplatelet agents) may be difficult if cancer surgery or treatment with chemotherapy that may seriously diminish platelet numbers, is imminent.

There is limited data on the cardio-protective effect

Table 1

Class	Mechanism of action	Typical use
1. Cytotoxic agents		
a. Anthracyclines – Doxorubicin, Daunorubicin, Epirubicin	Intercalate into nuclear DNA, impair topoisomerase II, cell transcription and division, producing Reactive-Oxygen-Species	Leukaemia and soft tissue tumours
b. Taxanes – Paclitaxel, Docetaxel	Polymerise tubulin leading to dysfunctional microtubules disturbing cell division	Breast and ovarian cancer
c. Other agents – 5 Fluorouracil, Capecitabine, Cyclophosphamide, Cisplatin	Bind to DNA causing crosslinking and ultimately apoptosis	Testicular, bladder, ovarian cancer
2. Molecular-targeted therapy		
a. Human epidermal growth factor 2 receptor (HER2) antibody - Trastuzumab	Humanized Immunoglobulin G1 monoclonal Ab directed against the HER2 protein	Breast cancer
b. Tyrosine kinase inhibitors – Lapatinib, Sunitinib, Imatinib	Stop protein activation by blocking signal transduction cascades	Breast, gastrointestinal stromal, renal cancer, leukaemia, non-Hodgkin's Lymphoma
c. Vascular endothelial growth factor (VEGF) inhibitors – Bevacizumab, Sorafenib, Axitinib	Inhibit tumour-associated angiogenesis mediated by VEGF and VEGF receptors.	Brain, kidney, lung, colon cancer
d. Other biologic agents – Rituximab	Monoclonal antibody acting against CD20 protein	Leukaemia, lymphoma

Table 1. Mechanisms of action and uses of common cardio-toxic chemotherapeutic agents. HER2 - Human epidermal growth factor 2 receptor, VEGF - Vascular endothelial growth factor.

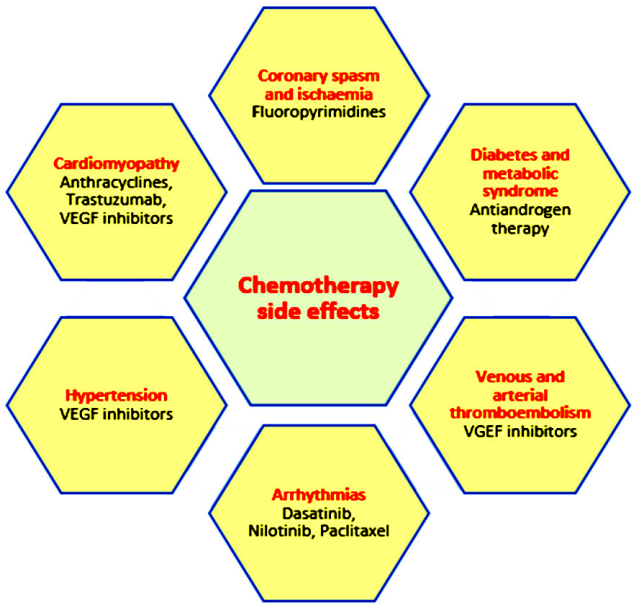


Figure 2. Cardiovascular side effects of chemotherapeutic agents. VEGF – Vascular endothelial growth factor

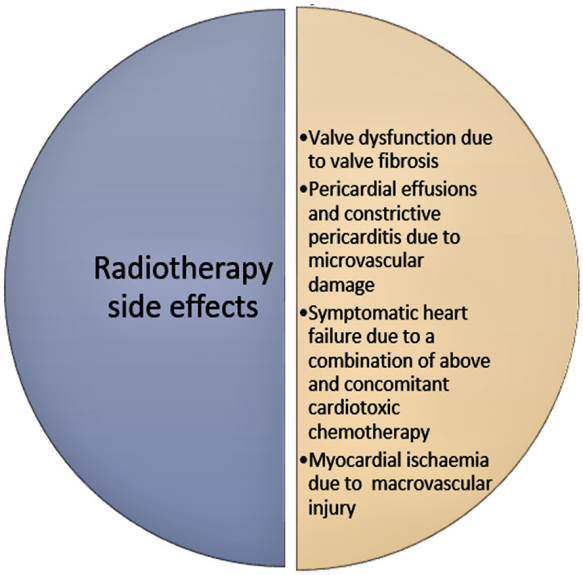
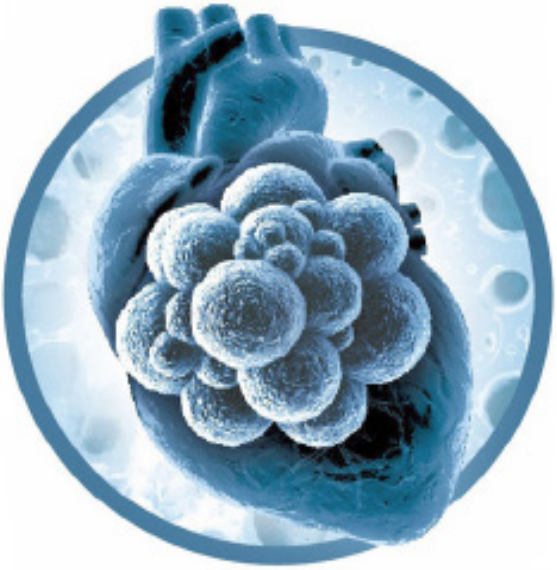


Figure 3. Cardiovascular side effects of cancer



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of Angiotensin Converting Enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and beta blockers in patients undergoing chemotherapy. Their use in this context (e.g. when the EF or strain values drop significantly with chemotherapy but still remain in the "normal" range) is unlicensed. Desraxozane (an iron chelator) has been shown to reduce doxorubicin-induced cardio-toxicity. 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 and its use is not widespread and although a previously a worsening in cancer outcomes was suggested, subsequent studies have not confirmed this potential.

The current UK perspective – services and training

There is an 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[2]. 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. This realization led to the appointment of the first consultant cardiologist in the UK with a special interest in cardio-oncology (the author).

Training programmes in Cardio-Oncology are well established in the USA with trainees from both Cardiology and Oncology undertaking these fellowships with the ultimate aim of developing Cardio-Oncology services with Cardiologists and Oncologists working together as a team[10]. Currently only a few hospitals in the UK offer Cardio-Oncology Fellowships. The aim of societies like the British Cardio-Oncology Society (http://bc-os.org/), International Cardio-Oncology Society (https://ic-os.org/) and American College of Cardiology (https://www.acc.org/Membership/Sections-and-Councils/Cardio-Oncology) is to expand training in Cardio-Oncology and ultimately develop formal training programmes.

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 investigations are key for detection of abnormalities and monitoring of patients with echocardiography the principal imaging modality
- Limited evidence showing the cardio-protective effect of ACE inhibitors, ARBs and beta blockers – new trials ongoing
- Current expansion in Cardio-Oncology services and training opportunities in the UK

Conflicts of interest:
The author is Education lead for the British Cardio-Oncology Society and on the Education Committee of the International Cardio-Oncology Society. He is also on the Cardio-Oncology Leadership Council of the American College of Cardiology.

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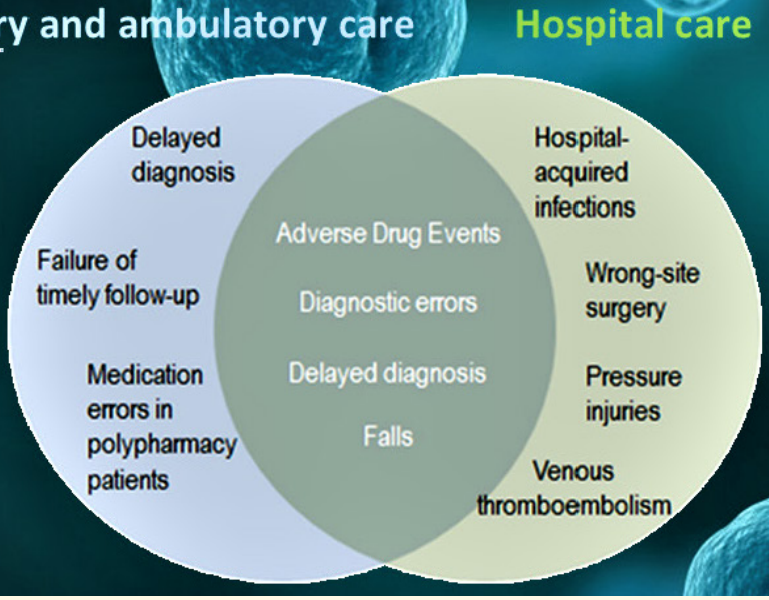
Improve patient safety by eliminating adverse events in health care settings

It is estimated that every year more than 300,000 patients acquire a healthcare associated infection (HCAI, HAI or nosocominal infection)as a result of care with in the NHS.



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