

### CARDIO-ONCOLOGY: AN EMERGING SPECIALTY

Incidence rates for all combined cancers have risen by 13% in the last 25 years, and are projected to rise by a further 2% in the next 20 years.<sup>1</sup> Advances in the treatment of malignant disease have led to increased survival in patients with cancer. However, mortality and morbidity related to cardiovascular side effects are becoming an increasing problem. In recognition of this, the specialty of cardio-oncology has developed rapidly over recent years, involving three distinct areas; the acute management of cardiovascular complications, for example, heart failure, arrhythmias, and acute coronary syndrome; the long-term screening of patients post-chemotherapy; and the planning of chemotherapeutic regimens in patients with established, or at high risk of, cardiovascular disease.

### RANGE OF CARDIOTOXICITIES

The most commonly observed cardiovascular side effect of anticancer therapy is left ventricular (LV) dysfunction. This is most frequently associated with anthracyclines (dose-dependent effect) and the monoclonal antibody trastuzumab (Herceptin®).

The mechanism of anthracycline-induced cardiotoxicity is poorly understood, but is thought to be free radical-mediated, causing myocyte apoptosis and LV thinning.<sup>2</sup> This leads to irreversible (type 1) LV impairment, which can occur acutely, or at an early (within first year of treatment) or late stage. It is important to note that 5% of patients with anthracyclines develop LV impairment and can present up to two decades after their therapy, therefore a history of childhood cancer should always be sought in the young adult presenting with symptoms of heart failure. Conversely, Herceptin is associated with reversible (type 2) LV impairment in up to 13% of patients, with the transient decline in LV ejection fraction (EF) typically seen during treatment.<sup>3</sup>

The mainstay of screening for these at-risk patients is transthoracic echocardiography. In recent years, newer techniques such as global longitudinal strain (a measure of myocardial deformation) and 3-Dimensional LV volumes have been demonstrated to be a more sensitive measure of left ventricular function, with abnormalities in these measures becoming apparent prior to a

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drop in the EF. Cardiac magnetic resonance imaging is a useful alternative in patients with poor echocardiographic windows. This modality provides a comprehensive assessment of the heart and is particularly useful when there is a clinical suspicion of fibrosis, for example, in patients with anthracycline-induced LV dysfunction.

Left ventricular dysfunction, whether subclinical or fulminant, may hinder the continuation of optimum chemotherapies. Therefore it is important to identify these patients as soon as possible so that cardio-protective medication can be commenced promptly to minimise cardiac damage and facilitate the continuation of chemotherapy. This has been demonstrated to improve outcomes in patients treated with cardiotoxic chemotherapy.<sup>4</sup> Beta-blockers and/or ACE inhibitors/angiotensin receptor blockers are indicated with an EF below 50%, a drop in EF of >10%, abnormal global longitudinal strain, or an abnormal troponin. Herceptin should be continued wherever possible, unless the EF drops below 40%.<sup>5</sup>

Hypertension, either pre-existing or iatrogenic, is common in patients with cancer. It is most frequently associated with tyrosine kinase inhibitors, such as sunitinib or bevacizumab, and/or as well as agents that are used for a variety of cancers. The mechanism underlying hypertension is unclear but is thought to be related to vascular endothelial growth

factor inhibition, which decreases nitric oxide production in resistance vessels.<sup>6</sup> Patients should be regularly screened for hypertension, and, when present, it should be treated in accordance with current guidelines.

Cardiac ischaemia is an uncommon side effect associated with 5-fluorouracil (5FU) and capecitabine (a 5FU precursor). It is usually the result of coronary artery spasm and resolves with withdrawal of the offending agent. As recurrence is likely, alternative treatment options are usually required for these patients. Other potential cardiovascular issues associated with chemotherapies are QT interval prolongation, pulmonary hypertension, pericardial disease, and arrhythmias.

Radiation-associated cardiotoxicity is most frequently seen in those who have been irradiated at a young age and so have had sufficient time to develop a clinically significant late cardiac injury. Radiotherapy to the chest can potentially affect any cardiac structure and patients can present with acute pericarditis shortly after their radiation therapy or with a delayed presentation many years later, due to chronic pericarditis, valvular heart disease, or ischaemic heart disease.<sup>7</sup>

### WHO IS MOST AT RISK?

There are several factors that increase a patient's risk of developing cardiotoxicity.

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## Box 1. Cardiotoxicity risk factors

### Patient related

- Age <18 years or >65 years
- Female sex
- Family history of premature cardiovascular disease (<50 years)
- Pre-existing cardiovascular problems (including hypertension, diabetes mellitus, hypercholesterolaemia)
- Lifestyle: smoking, excess alcohol intake, obesity, sedentary lifestyle

### Treatment related

- Concomitant use of other chemotherapies
- Prior anthracycline use (risk is dose-dependent and increases with cumulative dose)
- Previous mediastinal radiotherapy

These are patient related and/or treatment related [Box 1].<sup>3</sup>

## SCREENING

Cardiology screening, usually in the form of transthoracic echocardiography (convenient and cost-effective), during oncology treatment is well established. However, the proportion of oncology patients surviving for many years after their diagnosis has increased considerably over recent years.<sup>8</sup> Raising awareness of potential cardiac disease in this group of patients is key to providing a high standard of care and follow-up. Primary care physicians should maintain a high index of suspicion and refer any patients with symptoms suggestive

of LV dysfunction to a cardio-oncology specialist. Patients who have received anthracycline-based chemotherapy or have been irradiated are at particularly high risk and should be periodically screened using echocardiography and/or biomarkers.

## THE CARDIO-ONCOLOGY CLINIC

Specialist services for oncology patients with cardiovascular problems are imperative for optimum patient care. Services should be multidisciplinary, involving cardiologists, oncologists, haematologists, cardiac and oncology nurse specialists, psychologists, and cardiac physiologists. The aim is to facilitate the continuation of optimum anticancer therapies while providing appropriate management of pre-existing and/or iatrogenic cardiovascular issues that arise. There are several international guidelines that outline best clinical practice,<sup>4,9</sup> although there are still gaps in our knowledge and further research is needed to enable clinicians to optimally manage this complex group of patients.

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