

Review

# Cardiotoxicity Following Cancer Treatment

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## ABSTRACT

More than half of those born after 1960 will develop cancer during their lifetime. Fortunately, owing to improved diagnosis and treatment, cure rates have risen steadily over the last three decades. With an increased survivorship, more will experience adverse effects of cancer therapeutics on the heart. As the oncologist's focus begins to encompass the issues of cancer survivorship, awareness of the management of cardiac toxicity would be prudent for all physicians looking after patients with cancer.

## INTRODUCTION

Cancer and heart disease are the two most common causes of death in Northern Ireland. As cancer survivorship increases, understanding of the links between cancer treatments and cardiovascular disease becomes crucial for all medical practitioners. As cure rates improve, increasing priority can be given to optimising quality of life rather than focusing on prevention of cancer recurrence. Patients may view the adverse effects of cancer treatment in equal concern with the diagnosis of cancer itself, and with the development of new anti-cancer therapies, physicians must be vigilant for the symptoms and signs of emerging cardiovascular problems.

The last decade has seen an exponential growth in the numbers of anti-cancer treatments available, especially systemic anti-cancer treatment (SACT) and radiotherapy. It is these two anti-cancer therapies that are implicated in the emerging field of cardio-oncology, whether the aim of cancer treatment is curative or palliative (Table 1). This article explores the relationship of these treatments to cardiotoxicity, the indicative signs and symptoms and the management options available.

## OVERVIEW OF ANTI-CANCER THERAPIES

Radiotherapy delivers energy via ionising radiation to neoplastic cell DNA in such a way that the resultant damage induces cell death preferentially in malignant tissue. Approximately 40% of patients diagnosed with cancer receive radiotherapy<sup>1</sup>. Radiotherapy may be delivered using external beam radiotherapy (EBRT) (Figure 1), sealed internal sources, for example gold seeds for prostate cancer, brachytherapy and unsealed internal sources, for example, radioactive iodine for thyroid cancer. The key principle of minimising normal tissue irradiation whilst providing the optimum dose to the cancer target dictates that factors such as tumour histology,

TABLE 1:

*Commonly used cardiotoxic anti-cancer treatments*

Cancer Treatment	Examples
Cytotoxic chemotherapy	doxorubicin, epirubicin, cyclophosphamide, 5-fluorouracil, cisplatin, paclitaxel
Targeted therapies	trastuzumab, sunitinib, pazopanib
Hormonal therapies	tamoxifen, anastrozole, letrozole, goserelin, enzalutamide, abiraterone
Radiotherapy	breast, lung, mediastinal lymphoma and oesophageal radiotherapy

dimensions and position are used in determining the choice of irradiation method. Since the 1960s, treatment of lung and breast cancer and lymphoma with thoracic radiotherapy has increased cardiovascular morbidity via radiation toxicity<sup>2</sup>. In general radiotherapy techniques which do not deliver radiation to the heart do not cause cardiotoxicity.

The mechanism of action of each of SACT agent depends on the family and the era that they originate from, with newer agents having quite different targets than more established treatments. Cytotoxic chemotherapy is the nomenclature used to describe drugs such as the anthracyclines (eg. doxorubicin) and antimetabolites (eg. 5-fluorouracil) which are generally non-specific and which cause apoptosis and cause cell death by altering key components of cellular metabolism or by directly damaging DNA.

Hormonal therapies, molecular targeting agents and immunotherapies are more specific in their mode of action. Their cardiotoxicity risk can occur via a number of mechanisms:

1. Direct 'on-target toxicity' if the molecular target in the

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cancer also serves an important role in cardiovascular biology (e.g. trastuzumab.)

2. Indirect 'on-target toxicity' if the molecular target in the cancer is also a modifier of cardiovascular risk leading to the accelerated progression of a second disease (e.g. GnRH agonists for prostate cancer which increase LDL and diabetes risk leading to atherosclerosis and increased risk of myocardial infarction.)
3. 'Off target toxicity' where the drug appears to inhibit a range of molecular targets, not only the principle target molecule in the cancer, and inhibition or activation these additional pathways imparts cardiovascular risk (e.g. sunitinib displays both on-target and off-target toxicity.)



Fig 1. A linear accelerator for EBRT

## EXAMPLES OF CARDIOTOXIC TREATMENTS

### External beam radiotherapy

#### Lung cancer

Curative intent radiotherapy is offered to patients diagnosed with stage I - III non-small cell lung cancer or limited stage small cell lung cancer who have a good Performance Status<sup>3</sup>. EBRT is often the treatment of choice for patients who decline, or are unsuitable for surgery. Recent progress in radiation technology has the potential to revolutionise lung cancer treatment, with advances such as stereotactic ablative radiotherapy reported to have comparable results with surgical resection<sup>4</sup>. Radiotherapy also has a role in the control of incurable lung cancer, which affected two thirds of the 1143 total cases diagnosed in Northern Ireland in 2012<sup>5</sup>.

As observed in the general population, patients who are male, older age, African-Caribbean background, have pre-existing cardiac disease or have other co-morbidities experience a greater risk of cardiovascular morbidity following thoracic irradiation<sup>6</sup>. It is difficult to precisely determine the direct impact of radiotherapy from other risk factors for cardiovascular disease in patients with lung cancer owing to the sizeable impact of smoking. Ischaemic heart disease is more common in patients with tumours of the left lung compared with the right, after radiation treatment<sup>6</sup>. Recently developed alternative methods of delivery of thoracic

radiotherapy have achieved increased survival rates and reduced treatment durations for patients without increasing long-term toxicity<sup>7</sup>.

#### Breast cancer

Given the very high local control rates seen in patients with early breast cancer, an increased emphasis on avoidance of toxicity is given. Breast cancer radiotherapy constitutes 30% of a radiotherapy unit's caseload<sup>8</sup>. Adjuvant radiotherapy is offered to patients diagnosed with early and locally advanced breast cancer (over a third of patients with breast cancer receive radiotherapy<sup>9</sup>). However, in previous large overviews of breast cancer using data collected over 40 years, the reduced breast cancer mortality attributable to adjuvant radiotherapy did not always translate into an overall survival gain, probably due to an increased cardiac mortality in patients receiving treatment to the left breast<sup>10,11</sup>.

Major coronary events after left-sided breast irradiation have a bimodal peak incidence, with many patients affected in the 4 years post-treatment, and others >20 years post-treatment<sup>10</sup>. It has been shown that unintended cardiac irradiation during left breast treatment occurs in almost one half of patients despite CT-based treatment plans excluding this area<sup>12</sup>. As seen with lung cancer, cardiotoxicity in breast radiotherapy is dependent upon laterality, with a cardiovascular mortality ratio of 1.33 (left breast versus right) for treatment delivered in the 1970s<sup>13</sup>. Women aged < 35 years are at greatest risk of radiation toxicity, with a 6.5 x lifetime risk of cardiovascular death compared with the general population<sup>14</sup>. Recent evidence suggests that for selected older patients, with low risk breast cancer, the cardiovascular risks of radiotherapy may outweigh the potential benefits<sup>15</sup>. The burden of cardiotoxicity in patients with breast neoplasms has decreased as a consequence of improvements in radiation technology and some investigators have found the effect of tumour laterality has been negligible since 1993<sup>16,17</sup>.

#### Other thoracic radiotherapy

Mantle radiotherapy describes the extended pattern of radiation fields used to target supra-diaphragmatic lymph node groups, often encompassing the mediastinal and hilar lymphatics. Hodgkin's disease patients, for whom mantle radiotherapy was primarily used in the past have a higher risk of developing calcific valvular disorders (both stenosis and/or regurgitation)<sup>18</sup>, myocardial infarction, cardiomyopathy and pericardial disease<sup>19</sup>. As a result, the relative risk of patients in this group developing heart failure is 4.9<sup>19</sup>. This group of patients are also at risk of symptomatic (usually syncope) and asymptomatic conduction abnormalities<sup>20</sup>.

A recent review of the limited data on oesophageal cancer found a crude rate of radiation cardiotoxicity in these patients of 10.8%<sup>21</sup>. Adverse effects in order of increasing incidence were pericardial effusion, ischaemic events and heart failure. A recent review of pacemaker and implantable cardiac defibrillator safety in radiotherapy has acknowledged that



certain energies of radiotherapy pose a risk of malfunction and clinical oncologists are awaiting an update in the relevant guidelines<sup>22</sup>.

### Systemic anti-cancer therapy

#### *Anthracyclines*

Drugs such as doxorubicin and epirubicin form disruptive cross-links between paired DNA strands. They have an important role in the chemotherapy regime for many cancers including breast, gastrointestinal and blood. Cardiotoxicity due to an anthracycline is seen in 5.4% of breast cancer patients, and has been viewed as dose-dependent and related to the cumulative dose given over time<sup>23</sup>. The increased cardiac event rate is usually observed many years after treatment and is related to a patient's pre-existing cardiovascular risk factors<sup>24</sup>. Under the age of 70, anthracycline cardiotoxicity most often manifests as heart failure in breast cancer treatment<sup>25</sup>. Alternative preparations of the drug can be used to reduce the risk. Liposomal infusions may be less harmful than boluses and cardioprotective agents may be co-administered to further reduce the effect (e.g. angiotensin converting enzyme (ACE) inhibitors, beta blockers, dexrazozane) have been used<sup>26,27</sup>. Another anthracycline, epirubicin has been associated with mild rises in troponin levels unrelated to ischaemic events in the month following infusion<sup>28</sup>.

#### *Trastuzumab*

Trastuzumab is a monoclonal antibody directed towards the HER2 epidermal growth factor receptor and is licensed for use in metastatic breast cancer patients with over-expression of this receptor<sup>29</sup>. The associated type of cardiac dysfunction differs from that seen with classic cytotoxic drugs in that it is observed early (i.e. within weeks of commencing treatment), in a range of severities, independent of dose and it has a mainly reversible pattern without any ultrastructure changes<sup>30</sup>. In a study of 179 breast cancer patients, 44% of patients developed a cardiac event (defined as New York Heart Association (NYHA) III or IV heart failure or a reduction in ejection fraction) during the year of treatment, and almost a tenth had a second<sup>31</sup>. A total of 7% patients in this study had their trastuzumab discontinued, though discontinuing treatment did not affect the rates of a second cardiac event occurring. Prior or concomitant radiation therapy doesn't influence trastuzumab cardiotoxicity<sup>32</sup>, but anthracycline therapy does<sup>33</sup>.

#### *Other SACTs*

Intercalating agents such as cyclophosphamide employ a similar mechanism of action to anthracyclines (disruption of DNA 'unzipping' in replicating cancer cells) and are associated with early heart failure (one week post-treatment) and haemorrhagic myocarditis<sup>34</sup>.

Antimetabolite drugs such as 5-fluorouracil (5-FU), have a number of mechanism of actions, but exert their main effect

by triggering apoptosis in malignant cells by a process called a thymineless death<sup>35</sup>. These drugs may cause acute chest pain during or shortly after administration which occurs through the mechanism of coronary artery vasospasm<sup>36</sup>. Recognition of this is important for patients on capecitabine and infusional 5-FU as on-ongoing administration of those agents must be stopped until the symptoms have settled and cardiac investigations are completed.

TABLE 2:

*Commonly used cardiotoxic SACT and their adverse cardiovascular effects*

Drug / Family of Drugs	Cardiotoxicities
Anthracyclines	Heart failure (late and irreversible)
Trastuzumab	Heart failure (early and reversible)
Cyclophosphamide	Heart failure (early), haemorrhagic myocarditis
Antimetabolites	Coronary vasospasm, acute coronary syndromes
Platinum	Acute coronary syndromes
Taxanes	Heart block, bradycardia, tachyarrhythmia
Bevacizumab	Hypertension, thromboembolism
Sunitinib, sorafenib, pazopanib	Hypertension, heart failure, myocardial infarction

Platinum-based intercalating agents may also cause this symptom. Unlike the pattern seen in antimetabolites, the risk continues for many years, and cisplatin can be detected in the serum at 20 years<sup>37</sup>.

Taxane drugs such as paclitaxel and docetaxel disturb the microtubules needed to separate original and fresh copies of DNA in the dividing cell. These are commonly used in ovarian and breast cancer treatment and have been linked to heart block, bradycardia and tachyarrhythmias with a cumulative incidence of 0.5%<sup>38</sup>.

Hormonal treatments have not been consistently shown to increase the risk of cardiac events despite interfering with lipid metabolism<sup>23</sup>.

Bevacizumab, an agent targeting vascular endothelial growth factor receptors used in colorectal cancer, has been linked to cardiotoxicity via hypertension and thromboembolism<sup>39</sup>. Sunitinib targets this receptor in renal cell carcinoma and was strongly associated with cardiotoxicity in one large study<sup>40</sup>. Over a tenth of patients experienced cardiovascular events including myocardial infarction and heart failure, over a quarter had an asymptomatic decrease in ejection fraction of 10% or more and almost one half of patients were diagnosed with hypertension following drug administration.

### DIAGNOSIS OF HEART FAILURE

Whilst oncological treatments may cause a range of adverse

cardiovascular conditions, the commonest is heart failure. Heart failure is a complex syndrome in which the ability of the heart to maintain the circulation of blood is impaired<sup>41</sup>. Approximately half of patients die within 4 years<sup>42</sup> however mortality rates are improving<sup>43</sup>.

Biomarkers of cardiac injury (e.g. cardiac troponin I concentration) have been shown to identify patients at risk for anthracycline cardiotoxicity and predict a poor response to cardiac therapy<sup>44,45</sup>. The finding of a significantly raised B-type natriuretic peptide level (BNP or its precursor fragment NT-proBNP) provides evidence of heart failure with high sensitivity<sup>46</sup>. Whilst not useful in an unselected cohort of patients receiving SACT, NT-proBNP trends can identify at-risk patients treated with anthracyclines<sup>47</sup>.

Echocardiography is an excellent tool for identifying the patient with heart failure. A reduction in left ventricular ejection fraction (LVEF) is a late finding and may occur only after a significant amount of myocardial damage has occurred. Advanced echocardiographic techniques such as global longitudinal strain measurement may detect left ventricular impairment earlier than conventional LVEF<sup>48</sup>. Deteriorations of 13.7% or more from baseline warrant continued increased clinical vigilance with fair sensitivity (88%) and specificity (71%)<sup>49</sup>.

#### TEXT BOX 1:

##### *Application of natriuretic peptides to CTRCD*

- raised natriuretic peptide level is evidence of heart failure (highly sensitive)
- elevated NT-proBNP after an anthracycline identifies patients at risk of CTRCD
- CTRCD is not limited to high-dose regimes
- persistent elevations after 72 hrs predict progressive decline in left ventricular failure
- raised levels are associated with a greater risk of developing trastuzumab CTRCD

## CANCER THERAPEUTICS-RELATED CARDIAC DYSFUNCTION

Cancer Therapeutics-Related Cardiac Dysfunction (CTRCD) is defined by the European Society of Cardiology (ESC) as a decrease in LVEF of 10% or more, to a value less than the normal range<sup>50</sup>. CTRCD can further be divided into those who develop symptoms of overt heart failure and those who have an asymptomatic decline in systolic function. The ESC also sub-classifies systolic dysfunction by the degree of reversibility following clinical intervention:

- Reversible (returns to within 5% of baseline)
- Partly reversible (>10% improvement, >5% below baseline)
- Irreversible (<10% improvement, >5% below baseline).

It is felt that the most important factor is demonstration of reversibility.

All patients should be treated with an ACE inhibitor/angiotensin II receptor blocker (ARB) and a beta blocker licensed for heart failure. Some of these drugs have been assessed specifically in CTRCD patients, and may be preferable to others in the same drug class, as not all agents seem to be beneficial<sup>51</sup>.

In patients with early evidence of left ventricular impairment during cancer treatment, introduction of ACE inhibitors and possibly beta blockers may be helpful to recover cardiac function, and offer cardioprotection against further cancer treatment if required - particularly those with a history of cardiac disease. Different strategies are currently employed in various specialist centres with Cardio-Oncology services, including surveillance with echocardiography and cardiac biomarkers, early detection and cardioprotection during chemotherapy or cardiotoxic targeted molecular therapies. Involvement of the Heart Failure Specialist Team is essential.

## TRASTUZUMAB

It is important to appreciate that the majority of the 44% patients developing cardiotoxicity after trastuzumab had mild

#### TEXT BOX 2:

##### *Recommended actions for patients undergoing cardiotoxic anticancer therapy*

BEFORE COMPLETING TREATMENT	AFTER COMPLETING TREATMENT
Be aware of the cardiotoxic potential of patients' anti-cancer treatment plan Investigate new or changing cardiovascular symptoms	
Ensure patients are aware of the potential for heart problems during/after cancer treatment  Monitor weight, lipid profile, glycaemic control during hormonal therapies  Update the Oncologist early with relevant investigation results and medication changes	Regular and relevant cardiac function testing no later than 6 months following high-risk treatments and if normal/asymptomatic  Approach metastatic and non-metastatic patients with identical monitoring  Liaise with a cardiologist if there is a suspicion of cardiotoxicity



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or no symptoms<sup>31</sup>. The implication of previous or concurrent anthracycline is also worth recognising - this triples the risk<sup>31</sup>. Whilst no study has been designed to test this link specifically, a recent very large population-based study indicates that sequential therapy (anthracycline followed by trastuzumab) is more dangerous (4 x hazard ratio) than concomitant treatment (2 x hazard ratio)<sup>52</sup>. It is postulated that the cumulative oxidative damage from an anthracycline is negatively modulated in the vulnerable by trastuzumab via its direct mechanism of action on the HER2 pathway and some data suggests that a delay in initiating trastuzumab allows the myocytes to recover before a “second hit”<sup>44</sup>.

New elevations in cardiac troponin I were commonly seen after the first cycle, resolved within 3 months with patients developing cardiovascular symptoms by 8 months. In the same study, baseline troponin elevation patterns (following cytotoxic chemotherapy and prior to trastuzumab) were consistent with the hypothesis that the conventional time to commence trastuzumab may be during a period of myocyte vulnerability<sup>52</sup>. Therefore abnormal troponin values should prompt clinicians to follow up symptoms actively whilst a Cardio-oncology opinion is awaited. There is less data about using BNP for diagnosis and prediction of CTRCD with trastuzumab, compared with anthracyclines. Exploratory analyses have established that NT-BNP can be raised in absence of impaired LVEF on echocardiogram<sup>53</sup>, suggesting LVEF is not sensitive enough to detect subclinical damage from SACT. The Australian CATS (Cardiotoxicity of Adjuvant Trastuzumab) study should address this need when it is reported<sup>54</sup>.

Protocols for managing trastuzumab cardiotoxicity have been developed<sup>55,56</sup>. In the event of a severe drop in LVEF or the development of clinical heart failure, cessation of trastuzumab is clearly indicated. For cases with mild subclinical dysfunction, continuation of therapy with careful LVEF monitoring and protective medical therapy may be appropriate. Figure 2 is the traffic light triage approach suggested by the National Cancer Research Institute<sup>55</sup>. The traffic light system guides clinicians when to increase monitoring, when to refer to Cardiology and when to continue/discontinue trastuzumab and ACE inhibitors.

The clinical outcome of trastuzumab cardiotoxicity is more favourable than anthracyclines and in many cases, re-challenge may be safely carried out<sup>44</sup>. In the PRADA study, patients randomised to cardioprotection with candesartan or metoprolol suffered less cardiotoxicity from trastuzumab with candesartan (no benefit from metoprolol observed)<sup>50</sup>. Future studies should seek to clarify the need for cardioprotection as trastuzumab becomes increasingly prescribed not only for breast but other tumour types.

**CONCLUSIONS**

Cardiovascular disease and cancer are very common treatable conditions. Survival rates for cancer have increased significantly over the last three decades. Increased

survivorship increases the chances of developing treatment related complications such as cardiovascular disease. Both oncologists and non-oncologists need to be aware of the clinical syndromes and the potential treatments available for cardiovascular disease related to cancer treatment. The development of new specialist Cardio-Oncology services can help oncologists, haematologists and primary care access specialist care for cancer patients before, during and after treatment with cardiotoxic therapy.

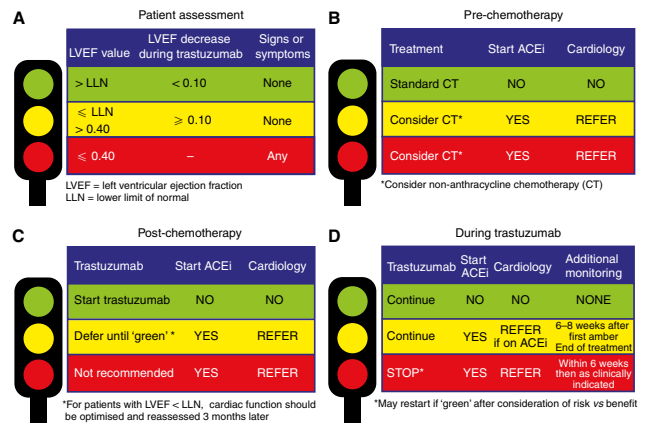


Fig 2. NCRi Traffic Light System

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