Asian Biomedicine Vol. 7 No. 3 June 2013; 311-318 **DOI: 10.5372/1905-7415.0703.181**

Review article

Cancer therapy induced cardiotoxicity: monitoring

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Background: Chemotherapies are highly effective in treating most cancers, but their use is limited by potential cardiotoxicity, the most serious of a wide range of adverse effects. The severity of these effects is related to the chemotherapy regimen, patient population characteristics and duration.
Objective: To review strategies to reduce cardiotoxicity in patients who receive chemotherapies.
Materials and Method: We reviewed and abstracted information from published peer review journals and provided examples from our relevant experiences.
Results: The severity of these effects is related to the chemotherapy regimen, patient population characteristics and duration. The incidence of cardiomyopathy because of chemotherapy varies and its onset can be acute (during or shortly after treatment), sub-acute (within days or weeks after completion of chemotherapy) or chronic (weeks to months after drug administration). A number of risk factors may predispose a patient to certain cancer therapy-induced cardiotoxicities. These can be identified, monitored, and possibly modified before initiation of cancer therapy so that cardiotoxicity can be prevented where possible.
Conclusion: Cardiotoxicity is an adverse event associated with many cancer therapy agents. The potential for cardiotoxic events should be recognized before therapy is started and serial monitoring of ventricular performance in order to minimize the possibility of irreversible cardiac damage.

Keywords: Cancer therapy, cardiotoxicity, monitoring

Of the currently available antineoplastic agents, anthracyclines have the most extensive data on surveillance for cardiotoxicity. Although several medical colleges around the world have proposed guidelines for monitoring anthracycline [1-3] and trastuzumab [6] cardiotoxicity, unified, evidence-based, consensus on an ideal monitoring strategy for antineoplastic cardiovascular surveillance has not been established. Endomyocardial biopsy has been viewed as the "gold standard" for anthracycline-induced cardiomyopathy; however, routine clinical surveillance strategies have frequently employed noninvasive cardiac imaging tools such as radionuclide angiography and echocardiography [1-7, 10]. Cardiovascular magnetic resonance (CMR) has emerged as the new noninvasive criterion standard appropriate for LVEF determination, with potential utility in cancer patients [13, 14]. Cardiovascular computed tomography, an approved tool for the evaluation of coronary artery disease in symptomatic low cardiac risk patients, is deemed inappropriate for routine serial evaluation of LVEF [29]. Possible roles for serum biomarkers, natriuretic peptides and troponins, and molecular imaging in risk stratification and serial monitoring of chemotherapeutic patients have been suggested by evolving research data [30-33].

Serial monitoring of ventricular performance and adherence to guidelines on surveillance are cost-effective. The limitations and benefits of the different monitoring techniques (**Table 1**) will be discussed.

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Endomyocardial Biopsy (EMB)

Endomyocardial Biopsy (EMB) has been viewed as the "gold standard" for evaluation of anthracycline-induced cardiomyopathy. It is reportedly very sensitive, as damage can often be seen at cumulative doxorubicin levels as low as 180 mg/m^2, and even after one dose, depending on individual sensitivity [1].

EMB samples only a very small area of the right ventricular endocardium; hence, it is also limited by false-negative results because of sampling error, and interobserver variability of the findings [3]. Most biopsy samples are taken from the right ventricle; although it is not yet clear to what extent the right ventricle is involved in the disease process. Biopsy may, therefore, even underestimate the severity of the myocardial changes. Its use is also limited by the specialist performing the procedure and interpreting the findings [1].

Table 1. Limitations and benefits of different monitoring techniques

Method	Benefits	Limitations
Endomyocardial biopsy	– Traditional 'gold standard' for evaluation of anthracycline-induced cardiomyopathy – Provided histological evidence of cardiotoxicity	– Invasive – False-negative results because of sampling error and inter-observer variability – Specialist required for performing and interpreting
Radionuclide ventriculography	– Noninvasive – Well-established and validated method to determine LVEF	– Radiation exposure – Low spatial and temporal resolution – LVEF measurements not sensitive for early detection of preclinical cardiac disease – No information of valve function or extracardiac structures – Contraindicated for pregnant or lactating women
Gated single photon emission tomography	– Simultaneous assessment of ventricular perfusion and function	– Radiation exposure – Needs further studies to determine utility for serial monitoring of LVEF among patients on antineoplastic agents
Echocardiography	– Noninvasive – No radiation exposure – Widely available – Provided information on cardiac morphology and function – Tissue Doppler imaging and myocardial strain rate can be considered valuable for early detection of LV dysfunction	– High intra- and inter-observer variability – Image quality dependent on presence of emphysema, obesity, left-sided breast implant, pectus excavatum) – LVEF measurements not sensitive for early detection of preclinical cardiac disease LVEF and FS affected by pre- and after-load
Cardiac magnetic resonance imaging	– Noninvasive – No radiation exposure – Considered criterion standard for left ventricular function – High reproducibility – High spatial and temporal resolution – Provides comprehensive information of myocardial function, perfusion and tissue characterization – Provides information of extracardiac structure – No need for exogenous contrast agent (if only LV function assessment)	– Contraindication in some patients with a pacemaker, metallic implant or claustrophobia – Limited availability – Limited use of contrast agent in patients with impaired renal function
Cardiac computed tomography	– Noninvasive – Image quality similar to CMR – Provide information of extracardiac structure	– Radiation exposure – Limited use of contrast agent in patient with impaired renal function
Biomarkers	– Troponin a highly specific and sensitive biomarker for detection of myocardial damage	– Limited clinical data
Cardiac stress test	– Evaluates contractile reserve of myocardium – Can detect cardiac abnormalities that remain occult at rest	– Semi-invasive – No consistent evidence that it enhances diagnostic sensitivity in cancer patients

The American College of Cardiology, American Heart Association, and European Society of Cardiology (ACC/AHA/ESC) joint scientific statement has limited EMB to use in patients with heart failure and suspected anthracycline cardiotoxicity (class IIa recommendation) [4].

Noninvasive cardiac imaging

Imaging techniques are conventionally applied in cardiotoxicity monitoring to determine LV ejection fraction (LVEF) or LV fractional shortening (FS). In many studies, cardiac toxicity is assumed if (a) LVEF drops more than 10% from baseline to values below 50%, (b) LVEF drops more than 20% from baseline despite still normal function, or (c) LVEF drops below 45%.

1. Cardiac Radionuclide Imaging

a. Radionuclide ventriculography (RVG): RVG is an established scintigraphic technique applied to assess changes of LV function in patients undergoing potentially cardiotoxic cancer therapy [1, 6]. It is a well-validated, accurate, and reproducible method to determine LVEF [7-10]. Assessment of cardiac performance by RVG is commonly performed by techniques of equilibrium intravascular labeling and equilibrium radionuclide angiocardiography (ERNA). With ERNA, labeling of the blood pool is accomplished with Tc-99m fixed to the patient's own red blood cells. The first pass radionuclide techniques were previously utilized.

In the landmark [1] among a high-risk cohort on doxorubicin (≥10% absolute LVEF decline from baseline to ≤50%, high cumulative dose of doxorubicin >450 mg/m^2, baseline LVEF <50%) on doxorubicin chemotherapy, it was concluded that monitoring resting LV function with RVG was associated with a low incidence of doxorubicin-induced congestive heart failure and adherence to appropriate guidelines reduced the incidence and severity of clinical congestive heart failure.

Swain et al. [11] demonstrated that LVEF measured by multiple-gated acquisition could not sensitively predict heart failure. Thus, RVG is suitable for detecting severe, early, cardiotoxicity or late-stage chronic disease, but lacks early prognostic markers. RVG—as well as gated single-photon emission computed tomography—frequently underestimates LV volumes, while overestimating EF; mainly for smaller ventricles (as seen in children and women), commonly associated with substantial errors in end-diastolic volume and end-systolic volume calculations [11-14]. Furthermore, compared with other techniques, the temporal and spatial resolution is low [14]. RVG is also limited by radiation burden of radioisotopes. RVG lacks the ability to visualize the myocardium.

b. Gated single photon emission tomography (SPECT): Gated SPECT (GS) is an alternative cardiac radionuclide imaging to RVG for measurement of LV volumes and ejection fraction usually performed as an integral assessment of stress/rest myocardial perfusion/function. Gated SPECT determination of LV volumes and ejection fraction is accurate, highly reproducible [15-17] and of significant prognostic value among patients with ischemic heart disease [18-20]. There is, however, limited data on utility of serial gated SPECT for LVEF in patients on antineoplastic agents.

2. Echocardiography

Echocardiography provides a wide spectrum of information on cardiac morphology and function. Parameters of systolic (LVEF, LVFS, and systolic wall thickening) and diastolic function (mitral inflow pattern E/A ratio, isovolumic relaxation time, and pulmonary venous flow pattern) can easily be measured with sufficient accuracy [21]. The lack of ionizing radiation, availability, and affordability have made echocardiography an attractive tool for assessment of LV performance. Notwithstanding, echocardiography for serial monitoring of LV performance may have significant challenges related to acoustic windows and reproducibility.

a. LVEF: Of the various echocardiographic surrogates of functional assessment of LV performance, LVEF is the most commonly used serial monitoring of patients on antineoplastic agents. LVEF determination from M-mode measurements, single and biplane 2-dimensional assessments have been validated, but reliance on geometric assumptions has limited accuracy for patients with symmetric ventricles [22]. Although 3D-echocardiography is more accurate and reproducible than 2D-measurements for LV volume and ejection fraction determinations with results comparable to multiple modalities including CMR and RVG, 3D-echocardiography is still subject to challenges because of poor acoustic windows in morbidly obese patients [23].

b. Diastolic function: Diastolic function assessment is considered an integral part of comprehensive evaluation of ventricular performance [24].

Limitations of echocardiography

In contrast to RVG, echocardiography does not involve the use of ionizing radiation and it is noninvasive, cost-effective, and widely available. Echocardiography is limited by variations of thoracic anatomy, which may interfere with imaging. In adults, emphysema, obesity, or the presence of a left-sided breast implant limit availability of acoustic windows, which may lead to poor quality images [25]. Another major concern is the high intra- and inter-observer variability of this technique. Diastolic parameters are highly sensitive to any change in the circulatory system and are therefore somewhat unspecific and difficult to interpret in patients with arrhythmia (**Figure 1**).

3. Cardiovascular magnetic resonance (CMR)

CMR is a valuable tool for assessing myocardial function, perfusion, and tissue characterization. CMR is considered the standard for measurement of ventricular volume and various parameters of global ventricular function [26], such as LVEF; because of three-dimensional image data sets that have been shown to be highly accurate for assessing the left ventricular ejection fraction, an important parameter used to identify cardiac dysfunction in chemotherapy recipients [26, 27]. As demonstrated among other participants with cardiomyopathy, magnetic resonance imaging has high reproducibility and can detect small changes in left ventricular ejection fraction [27]. This technique can also provide data on valvular structures and the pericardium. Unlike RVG, CMR does not use ionizing radiation such that functional images may be acquired without a peripheral intravenous access. Furthermore, myocardial tissue characterization in appropriate patients can help elucidate the etiology of cardiomyopathy (**Figure 2**).

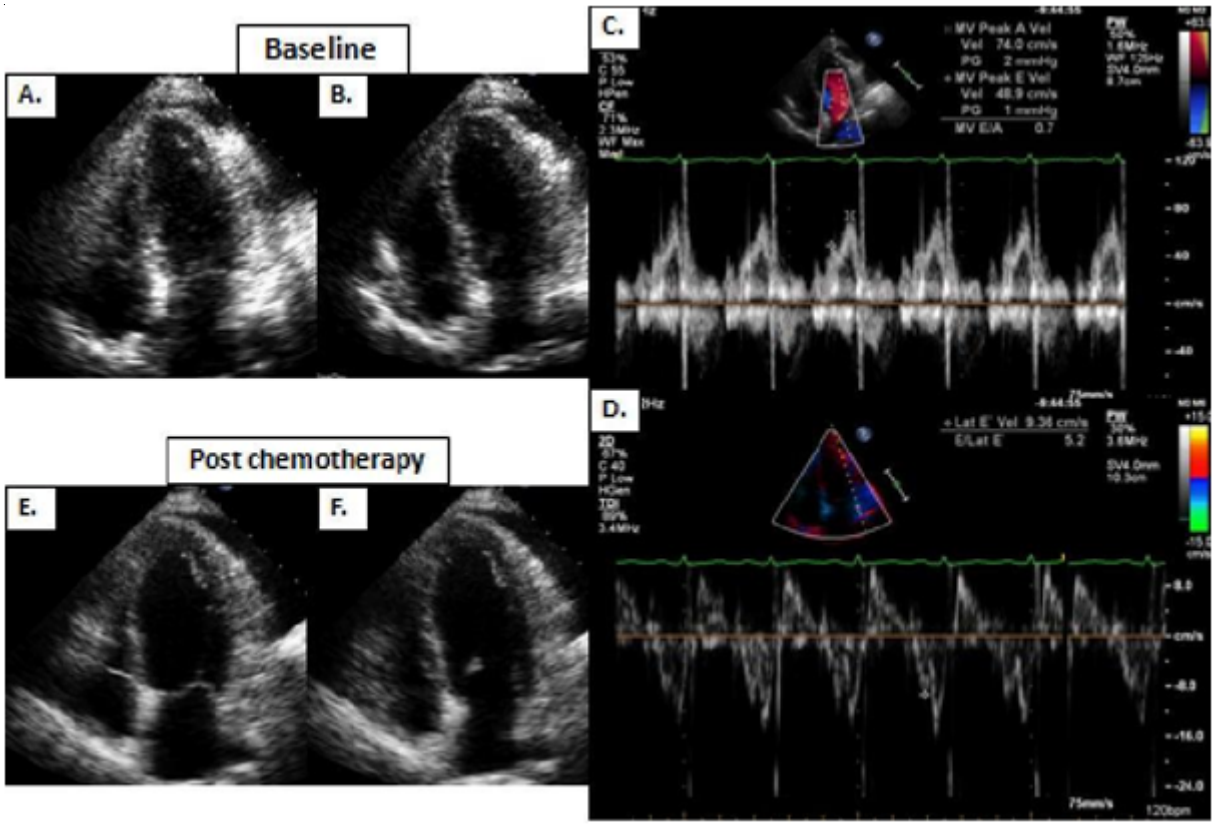

Figure 1. A 52-year-old woman diagnosed with breast cancer receiving anthracyclines. Baseline 4 chamber view of 2D-echocardiogram in end systole and end diastole. **A and B:** Normal LVEF (LVEF = 50%, LVEDV = 47 ml, LVESV = 25 ml). **C and D:** Baseline mitral inflow to annular ratio (E/e′)—obtained using routine pulsed-Doppler of the mitral inflow and pulsed-tissue Doppler of the lateral mitral annulus—demonstrated mild diastolic dysfunction, impaired relaxation of the left ventricle (mitral peak A velocity = 74 cm/s, mitral peak E velocity = 48.9 cm/s, mitral E/A = 0.7, E/e′ = 5.2). Postchemotherapy 4 chamber view of 2D-echocardiogram in end systole and end diastole. **E and F:** A reduced LVEF (LVEF = 29%, LVEDV = 62 ml, LVESV = 44 ml). Mitral inflow and TDI were uninterpretable because of arrhythmias causing fusion of the E and A waveforms. E: peak early filling velocity, A: velocity at atrial contraction, e′: velocity of mitral annulus early diastolic motion, TDI: tissue Doppler imaging.

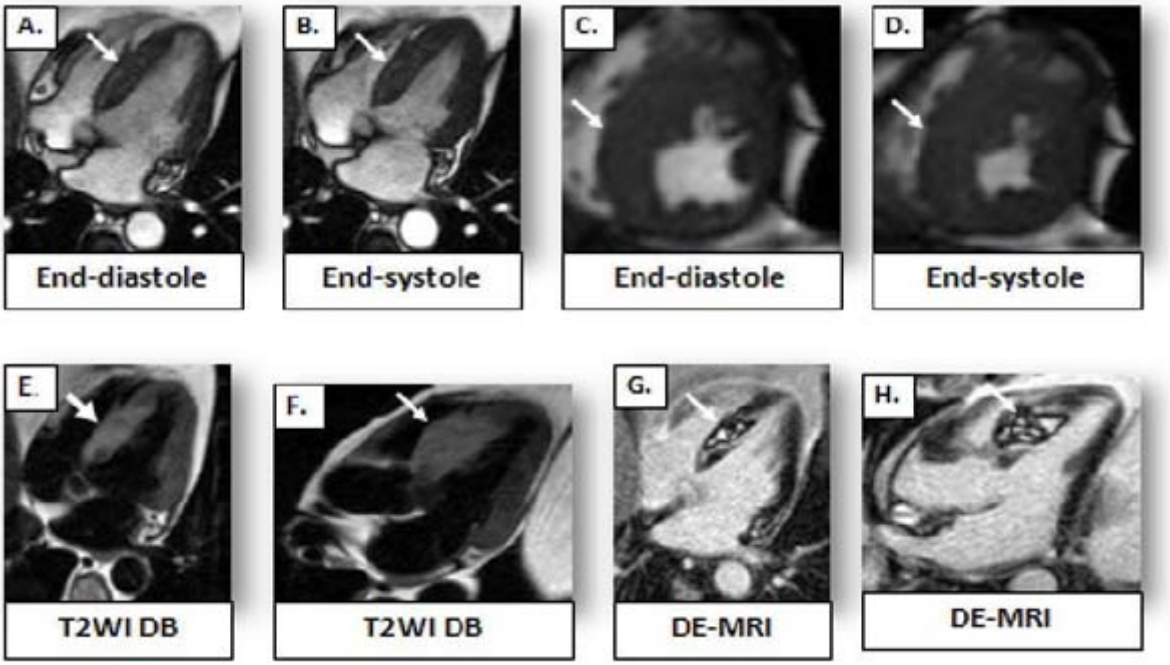

Figure 2. 61-year-old man with no known coronary artery disease who presented with STEMI status post-catheterization with patent coronary arteries. He was diagnosed with large B cell lymphoma status post-high-dose of 5-fluorouracil and cyclophosphamide. Cine MRI, using white blood cell technique of 4 chamber (**A, B**) and midventricular short-axis slice (**C, D**). T2-weighted dark blood images (T2WI DB) and delayed enhancement (DE-MRI) of 4-chamber (**E, G**), and 3-chamber (**F, H**) views demonstrated wall thickening, hypokinesia, edema, hemorrhage, and delayed enhancement throughout the entire interventricular septum (arrows).

CMR can also detect important extracardiac findings that may be relevant to the management of cancer patients. Unexpected extracardiac findings detected by CMR were observed in up to 80% of participants in one study [28]. CMR can reveal important findings and abnormalities in extracardiac structures contained in the scanned volume without additional expense, which would be even more beneficial to cancer patients.

The limitations of CMR include (a) its not being widely available, (b) it cannot be performed in patients with any contraindication to CMR imaging/scanning, including having intraorbital metal, claustrophobia, ferromagnetic cerebral aneurysm clips, pacemakers, defibrillators, functioning neurostimulator devices, or other implanted electronic devices, and (c) the limited use of contrast agents in patients with impaired renal function.

4. Cardiovascular computed tomography (CCT)

CCT is based on a multislice acquisition of data with only one or two scanning units to accurately depict the fast moving structures of the heart. Image quality with CCT is similar to CMR and can provide comprehensive evaluation of coronary artery anatomy, valvular anatomy and pericardium, but its temporal resolution is limited (**Figure 3**).

The function assessment possibilities are limited; however, previous studies have shown that CCT can evaluate LVEF with a higher accuracy than CMR [29]. As with CMR, CCT has the benefit of providing extracardiac findings. To date, no data are available from the clinical setting on chemotherapy patients because of high radiation exposure and limited data in this setting, so CCT is not considered an appropriate test for serial monitoring of LVEF in cancer patients.

Biomarkers

There is significant interest in developing simple and reproducible methods with strong predictive value for identifying patients at risk of therapy-induced myocardial damage. Current data suggests that circulating markers (such as troponins and natriuretic peptides) could serve as such monitoring tools [30-32].

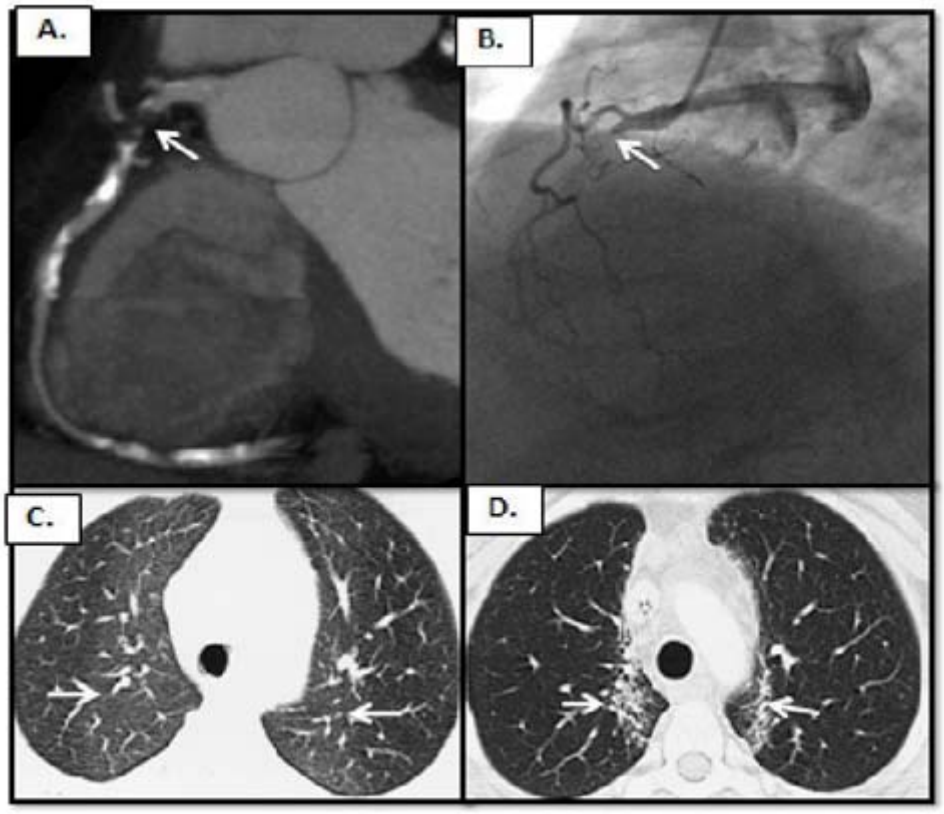

Figure 3. CT angiography of coronaries was performed in a 60-year-old male diagnosed with Hodgkin lymphoma (status postmediastinal irradiation) who presented with intermittent chest pain. MIP (maximal intensity projection) reconstruction. **A:** Soft plaque with total occlusion of the proximal right coronary artery. Invasive coronary angiography. **B:** Total occlusion of the proximal right coronary artery (arrow). CT scan obtained with narrow window settings 16 weeks after completion of radiation therapy. **C:** Subtle, paramediastinal, ground-glass attenuation in the upper lobes (arrows), a finding indicative of radiation pneumonitis. A CT scan obtained 11 months after completion of radiation therapy. **D:** Organization of the radiation pneumonitis into the typical paramediastinal pattern of fibrosis (arrows).

Surveillance of cancer survivors (>2 years)

Current guidelines

The aforementioned sections have indicated excessive cardiovascular morbidity and mortality among cancer survivors. Current surveillance guidelines have focused on children previously exposed to chemo and radiation therapy, so no consensus on cardiovascular screening of adult cancer survivors has been developed. The Framingham score—clinically used for cardiovascular risk assessment—does not include prior exposure to chemotherapy or radiation. We offer the following solutions for cancer survivors with a history of chemotherapy especially anthracycline;

a. Determine global LVEF.

b. Consider the fasting lipid profile as specified by the US Preventive Task Force Guidelines for Treatment of Hyperlipidemia according to the ATP III Panel Recommendations [34].

c. Explore the role of serum CRP among patients with acceptable lipid profile, given recent results of the JUPITER trial [35].

d. Consider the potential role of CCT in patients previously exposed to radiation.

e. Determine the calcium score/CTA: the ACC/AHA Guidelines recommend a calcium score for further risk stratification among asymptomatic patients at intermediate risk. Radiation-associated CAD trends to be ostial or proximal disease: current low radiation-dose CTA has excellent diagnostic accuracy and a negative predictive value for ostial and proximal disease.

f. Consider the potential role of CMR: With imaging strengths as previously described, CMR can be used to accurately document global LV function

among cancer survivors. CMR angiography using current 3D techniques has excellent accuracy for detection proximal/ostial disease, which is prevalent among cancer survivors with radiation associated CAD.

Conclusion

Cardiotoxicity is an adverse event associated with many cancer therapy agents. The potential for cardiotoxic events should be recognized before therapy is started; to minimize the possibility of irreversible cardiac damage. A number of risk factors may predispose a patient to certain cancer therapy-induced cardiotoxicities. These can be identified, monitored and possibly modified before initiation of cancer therapy so that cardiotoxicity can, where possible, be prevented. Six strategies to reduce the cardiotoxicity of cancer therapy have been recommended. These are not intended to be prescriptive, but their aim is to help clinicians identify cancer therapy receiving patients at increased risk of cardiotoxicity, so that appropriate decisions regarding the use and monitoring of cancer therapy can be made.

Acknowledgements

The authors thank the Faculty of Medicine, Khon Kaen University for its support and Mr. Bryan Roderick Hamman and Mrs. Janice Loewen-Hamman for their assistance with the English-language presentation of the manuscript.

The authors have no conflicts of interest to report.

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