EDITOR'S PICK

Our Editor's pick for this issue is a thought-provoking paper from Ronald J. Krone, discussing the role cardio-oncology has in protecting the heart in cancer patients. Collaboration between oncologists and cardio-oncologists is imperative in developing cardiologists with expertise in understanding the impact that various cancer regimens have on the heart and to develop programmes to manage or prevent heart damage, ultimately ensuring better quality of life in the cancer patient.

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PROTECTING THE HEART IN CANCER PATIENTS: THE ROLE OF CARDIO-ONCOLOGY

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Disclosure: The author has declared no conflicts of interest.
Received: 30.01.17 **Accepted:** 04.09.17
Citation: EMJ Cardiol. 2017;5[1]:47-52.

ABSTRACT

Cardiac disease often impacts cancer therapy, from direct toxicity of cancer therapeutic agents to the coronary endothelium, the myocardium, heart valves, and other structures. This has spawned the development of cardio-oncology programmes, emphasising collaboration between oncologists and cardio-oncologists in order to develop cardiologists with expertise in understanding the impact of various cancer regimens on the heart and developing programmes to manage or prevent heart damage. Cardiac disease and cancer both become more common as people age, as such cardiac disease, including coronary disease, should be screened for and risk factors treated when possible. Cancer-caused cardiac damage is much more responsive to therapy if treated early, so protocols for monitoring heart function to identify early injury need to be established and followed. Newer measures of ventricular function can identify heart injury before a reduction in ejection fraction to permit early initiation of therapy, and protocols to utilise these measures need to be incorporated into routine surveillance. Research is underway to evaluate regimens for cardiac protection prior to the cancer therapy, but at present, the data do not permit broad recommendations.

Keywords: Cardiology, medical oncology, cancer therapy, cardio-oncology, cardiotoxicity, chemotherapy, myocardial dysfunction, surveillance, antineoplastic agents, cardiovascular agents, cardiovascular diseases, humans.

INTRODUCTION

The growing awareness of the potential for serious cardiotoxicity of cancer treatment and the specific problems of managing cardiac disease before, during, and after cancer therapy[1,2] has led to the emergence of cardio-oncologists (or the oncocardiologists[3]): cardiologists with special interest and expertise in partnering with oncologists to develop systems to permit maximum treatment of cancer while minimising the potential severe cardiac toxicities that have been seen in the past. There has been considerable research aimed at understanding the mechanisms of toxicity of treatments[4] and developing strategies of management.[5-7] A key principle has been close co-ordination between cardiologists and oncologists with the common goal being to minimise or prevent

heart problems from interfering with the best management of the cancer.[8-10] This has spawned the development of cardio-oncology societies around the world.[11,12] Multiple symposia are held annually to bring together cardiologists, oncologists, and the latest advances in this field.[13] The goal of the cardiologist is not just to protect the heart, which would be achieved by simply stopping chemotherapy. The goals have to be to keep the heart protected so that the cancer therapy is not compromised and to work out surveillance for the survivors, so late deterioration can be identified and managed to maintain the hard-won quality of life.

SCREENING FOR CORONARY DISEASE IN CANCER PATIENTS: RATIONALE AND PRACTICE

Cardiac disease and cancer incidences both increase as people age.[14] The likelihood of a cardiac event can be reduced with risk reduction.[15,16] Evaluation of coronary risk primarily means screening for elevated cholesterol, diabetes, hypertension, and cigarette smoking,[17] as well as family history of premature coronary disease, peripheral vascular disease, and coronary calcification.[18] Calcification of coronary arteries can be approximated on chest computed tomography (CT) scans, and peripheral vascular disease by a careful history and evaluation of the carotid and femoral arteries for bruits. Reducing cardiac risk in addition to interdiction of cigarette smoking and control of diabetes means aggressive control of blood pressure and lowering of low-density lipoprotein cholesterol, if elevated, with statins.[15] Statins have been shown to reduce the risk of coronary events, both in terms of secondary prevention (i.e. patients with existent disease)[19] and for primary prevention.[18,20] An electrocardiogram should be obtained prior to initiating therapy, as it may disclose unsuspected cardiac disease and can be used as reference later in therapy. Patients about to undergo potentially toxic chemotherapy need a baseline evaluation of left ventricular function, and protocols for follow-up have been described.[21,22]

PROTECTING THE HEART DURING CHEMOTHERAPY

Strategies to protect the heart during chemotherapy have recently been discussed in detail.[7,11,22-24] Cardinale et al.[25] showed that the initiation of heart failure therapy in patients with cardiac dysfunction secondary to doxorubicin therapy is much more effective if started within 3 months of the development of heart failure, since none of the patients responded ≥6 months after its development. They showed that the cumulative cardiac event-free rate was >90% over 2 years in responders and ≤35% for partial or no responders.

MONITORING CARDIAC FUNCTION

Waiting for symptoms alone is unreliable as a strategy to identify patients early, because physicians pick up only a fraction of the symptoms experienced by patients.[26] The gold standard for monitoring is measurement of the left ventricular ejection fraction, although it is a late representative of myocardial damage.[21,22,24] While multigated acquisition scans were originally used for this purpose, newer imaging modalities give more information and also provide information earlier than the reduced ejection fraction, which occurs relatively late and with more severe injury. Cardiac magnetic resonance imaging (CMR) is considered the gold standard for cardiac measurements and, of the modalities available to make these measurements, is the least susceptible to acquisition errors.[27] In addition, with the infusion of gadolinium, CMR can evaluate the myocardium for fibrosis, inflammation, and oedema, as well as segmental wall motion abnormalities and myocardial strain. It is an excellent measure of ventricular volume; however, it is expensive, has limited availability, and cannot be used in some patients, such as those who are extremely obese or claustrophobic. Two-dimensional echocardiography is widely available, but quality of the results can be a problem.[27] The need for precision in the measurement of left ventricle (LV) function is critical in the oncology field, especially because important treatment decisions are based on these results. The quality of the echoes varies considerably in different laboratories and if the oncologist uses echo values as guides, they need to be sure that the quality is high and that the echo laboratory is focussed on careful results, with echo contrast used in all but unusually clear cases. The echocardiogram also provides information about pulmonary systolic pressure and fluid state by examining the inferior vena cava. Newer machines can acquire ventricular strain data, as well as providing an automated three-dimensional (3D) measure of ejection fraction. 3D echo has been shown to be more reproducible and correlates better with magnetic resonance imaging (MRI).[27] Changes in global

longitudinal strain and tissue Doppler imaging precede changes in ejection fraction, allowing an earlier recognition of LV dysfunction[28] and introduction of therapy.

Serum biomarkers monitored during treatment have been shown to identify patients at risk for deterioration. Cardinale et al.[29] proposed the use of troponin I (TnI) levels to monitor LV injury during doxorubicin administration. The early presence and persistence of a positive TnI identified patients destined to develop cardiomyopathy. Brain natriuretic peptides have been advocated as a biomarker for early LV injury,[30] but their sensitivity to establish early LV injury is not clear,[31] and at present they are not recommended.[22] The study from Fallah-Rad et al.,[28] however, indicates that these biomarkers are not a substitute for direct cardiac imaging in patients treated with trastuzumab, which may cause less myocardial death then dysfunction. The specificity of an elevated TnI may be adequate to justify the institution of cardioprotective measures.

TREATMENT FOR CARDIAC DYSFUNCTION DEVELOPING DURING CHEMOTHERAPY

Current treatment for heart failure includes beta-blockers (carvedilol, metoprolol succinate, bisoprolol, and nebivolol), angiotensin converting enzyme inhibitors, or angiotensin receptor blockers and aldosterone blockers, and is designed to protect the heart from the body's deleterious hormonal response to heart failure.[32-36] This approach can improve or reverse the LV depression in a high percentage of cases.[37] Perhaps decreasing hormonal stress on the heart allows the damaged heart to heal, as detailed by Topkara et al.[38] The combination of an angiotensin receptor blocker (valsartan) with a neprolysin inhibitor has been shown to be more effective than enalapril alone in improving heart failure,[34,39] and ivabradine, an inhibitor of the I_f current in the sinus node, selectively slows heart rate and reduces the composite endpoint of death and rehospitalisation in patients with increased heart rate and reduced ejection fraction.[35,40] The effect of these agents in heart failure caused by chemotherapeutic toxicity has not been studied. Ivabradine is particularly intriguing, because sinus tachycardia is common in cancer patients, but studies in this group have not been done.[41] Of course, the development of LV dysfunction has serious implications for cancer treatment, since in most cases treatment has to be interrupted or altered.

PRETREATMENT WITH CARDIOPROTECTIVE MEASURES

Due to the importance of preventing cardiac depression and the implications for the continuation of cancer therapy, as well as avoiding the serious long-term consequences of serious cardiac damage, there is great interest in preventative therapy with cardioprotective agents. The current state of the art practices have been reviewed by Curigliano et al.[6] and Hamo et al.[7]

Beta-blockers

Beta-blockers differ in their mechanism of actions and their effectiveness in this role of protecting against LV depression from chemotherapy varies. Carvedilol, a non-selective beta-blocker with antioxidant activity,[42] and nebivolol, a cardio-selective agent with antioxidant activity and a nitric oxide donor,[43] have been shown to reduce the depression caused by cardiotoxic anticancer drugs, but metoprolol did not protect in several studies.[44,45] The effects of carvedilol against doxorubicin cardiotoxicity have been shown to have a protective effect against mitochondrial dysfunction induced by doxorubicin, as well as carvedilol's antioxidant properties. These effects were not shared with propranolol,[46] but have also been shown to be a feature of nebivalol.[47] This suggests that many of the protective effects of carvedilol, and perhaps nebivolol, are not the result of their beta-blocking activity and may explain why carvedilol appears more effective than other beta-blockers. A randomised study, evaluating bisoprolol and perindopril in patients with breast cancer treated with trastuzumab, showed that both drugs attenuated the decrease in ejection fraction but did not attenuate the dilatation of the LV,[48] so these drugs cannot be assumed to be protective in the prophylactic setting.

Angiotensin-Converting-Enzyme Inhibitors

Several studies with angiotensin-converting-enzyme inhibitors have been published, primarily utilising enalapril with positive results, although one large study with 125 patients showed no effect.[45] The combination of enalapril and carvedilol prevented LV deterioration with doxorubicin. Valsartan,[49] telmisartan,[50] and candesartan[44] have all shown protective efficacy.

Spironolactone

Spironolactone has been shown to protect myocardial function when given simultaneously with doxorubicin.[51] However, the potential relative increase in oestrogens due to the antiandrogen effects of spironolactone are a theoretical concern.

Eplerenone

Eplerenone may be an alternative, but there are no data as yet on this subject.

Statins

Statins have been explored as a possible cardio-protection agent.[52,53] Lovastatin administered to mice attenuated doxorubicin proliferation of mitochondria, reduced increased marker for stress, and reduced the decreased LV function.[54] Several studies give some credence to this relationship. In a propensity match analysis, 67 women taking statins were compared to a control group of 134 women not taking statins and the authors found fewer heart failure hospitalisations within the statin-taking group.[55] In a second comparison with 51 patients, using cardiac MRI as the endpoint, the 14 patients taking statins showed no decline compared to the patients not taking statins.[56] A randomised clinical trial using atorvastatin 40 mg compared to placebo showed no difference to the primary endpoint of ejection fraction <50% after 6 months; however, there were some late study effects (less increase in LV systolic and diastolic diameter and a sudden decline in LV ejection fraction).[53] One should note that the lipophilic atorvastatin and simvastatin are metabolised by the CYP3A4 pathway and may interact with other chemotherapeutic agents to modify the metabolism of both. The hydrophilic statins, pravastatin, rosuvastatin, and pitavastatin do not have this problem.

Dexrazoxane

Dexrazoxane, a drug developed to chelate iron and prevent the formation of free radicals that disrupt many aspects of the cellular architecture, has been found to interfere with topoisomerase (TOP)2α in tumour cells and TOP2β in cardiac cells. By blocking the effects of doxorubicin on TOP2β, dexrazoxane is cardioprotective, but there remain concerns that it may also block the tumouricidal effects on TOP2α.[4] At present, in adults the administration of dexrazoxane is given after 300 mg/m^2 of doxorubicin because of concerns of loss of efficacy. Additional studies are sorely needed to clarify this concern.[57,58]

The approach to pretreatment prophylaxis is described in the recent 2016 European Society for Cardiology (ESC) Position Paper.[22] They restrict prophylactic treatment to patients at high risk of developing cardiac toxicity; i.e. those with pre-existing cardiac disease or at high risk of coronary disease or previous potentially cardiotoxic therapy. Administration of cardioprotective therapy, an alternative anthracycline, with modified delivery such as liposomal doxorubicin or continuous infusion is recommended for those at high risk. New analogues of doxorubicin targeting only TOP2α are being developed and are in the early phases of testing. The execution of prophylactic treatment using these agents is limited by the frequent development of side effects, namely hypotension and orthostatic hypotension, and as such there is no consensus about protocols for identifying early toxicity. The sensitivity and specificity of the biomarkers has not been established and echocardiography is expensive. The ejection fraction is recognised to be a late expression of toxicity, so there is considerable support for using earlier markers of decreased function, namely global longitudinal strain and possibly diastolic dysfunction, as a trigger for prophylactic therapy to better justify the side effects and effort needed to monitor the pressure.[21,59]

MONITORING TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors targeting vascular endothelial growth factor (VEGF) signalling pathways (sorafanib, sunitinib, bevacizumab, and cediranib) are associated with severe hypertension in up to 42% of treated patients, often developing within a few days of treatment. Aggressive pressure control often permits continued chemotherapy with these effective agents, but if untreated the hypertension can lead to heart failure. This effect is similar to that described by Topkara et al.[38] in mice. They developed a transgenic mouse that developed heart failure when exposed to inflammation, which activated a proinflammatory pro-gene. When inflammation was suppressed by doxycycline, a decrease in cardiac function did not occur, although some fibrosis was noted on electron microscopy. However, when this heart was exposed to severe hypertension (by an aortic constriction) exaggerated hypertrophy and increased mortality developed compared to normal mouse littermates. The heart in VEGF treatment has some injury, which is expressed as LV dysfunction when

stressed by the extreme hypertension; therefore, early monitoring and treatment is essential.

CONCLUSION

Cardiac toxicity with chemotherapeutic agents is common and early treatment of the cardiac dysfunction is likely to be effective, whereas delay, even as little as 6 months, will limit results. To minimise this serious problem, the cardio-oncologist should first calculate the risk of underlying coronary disease and treat any extant risk factors. Then, based on cancer treatment, identify persons at high risk of developing cardiotoxicity and consider prophylactic therapy with the agents described. In the patients judged to be at low risk, careful surveillance with biomarkers and newer echocardiographic indicators of dysfunction strain and tissue velocity. High-quality echocardiograms, ideally utilising 3D images for calculation of ejection fraction and myocardial strain, need to be developed and quality controlled.

Treatment with heart protective therapy, if deferred, can then be initiated at the earliest sign of LV depression, before the damage progresses to the point that the cancer therapy has to be interrupted. Patients taking tyrosine kinase inhibitors targeting VEGF should be very closely monitored by the development of hypertension, and treated aggressively and promptly. Close co-operation between cardiologists and oncologists can make it possible to administer cancer therapy minimising the collateral damage to the heart. This can pay big dividends in the quality of life in the cancer survivor. Needless to say, more data are needed of this unique population to better develop therapy to meet these goals.

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