

Heart failure resulting from cancer treatment – still serious but an opportunity for prevention

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Success in the diagnosis and treatment of many cancers has resulted in a growing population of people living either cured of cancer or with their cancer controlled as a chronic disease by long term treatment. This success story in modern medicine has created a new problem with some survivors developing cardiovascular disease as a result of their cancer treatment.⁽¹⁾ This is not a surprise given the biology of cancer and the strategies for treating cancer which frequently inhibit molecular pathways or cellular organelles critical for healthy cardiac function.

One of the most serious consequences of cardiotoxic cancer therapy is heart failure which can lead to significant morbidity and premature mortality.⁽¹⁻³⁾ A growing number of cancer therapies may cause cardiac dysfunction, either via direct myocardial injury, or by inhibition of essential molecular pathways for normal cardiac function in healthy hearts or pathways which serve to stabilise function in individuals with pre-existing cardiovascular disease. The most common and best understood is anthracycline cardiotoxicity, with drugs such as doxorubicin and epirubicin still the cornerstone of treatment for breast cancer and various haematological malignancies. Anthracyclines initially cause a functional impairment of ventricular myocardium, which with increasing dose and time can lead to irreversible damage via myocytes necrosis, apoptosis and replacement fibrosis. Radiation to the heart can also cause direct toxicity leading to heart failure, both via direct myocardial damage and indirectly via myocardial infarction from radiation-induced coronary artery disease, valvular heart disease and pericardial constriction.^(1, 4) The list of newer cancer drugs causing heart failure is expanding rapidly, including trastuzumab and HER2 targeted treatments, tyrosine kinase inhibitors targeting the vascular endothelial growth factor receptors or the BCr-Abl fusion protein, proteasome inhibitors and the new checkpoint inhibitors.

When compared to other forms of heart failure, cancer therapy-induced heart failure has historically been considered one of the more severe forms, due to resistance to standard heart failure medical therapy, and portending a worse prognosis. The seminal paper from Felker and colleagues in 1230 patients with a new diagnosis of 'heart failure due to unexplained cardiomyopathy' reported the long term outcomes in their heart failure cohort from the previous 15 years.⁽²⁾ The cohort of

patients with anthracycline-induced cardiomyopathy were a small subgroup (n=15) with one of the worst prognosis. They had a 3.46 fold higher mortality at a median 4.4 years follow up compared to idiopathic dilated cardiomyopathy cases. Since that paper many advances in the treatment of heart failure with reduced ejection fraction have been made,(5) and therefore knowledge regarding outcomes in more contemporary populations has been lacking.

In this issue of *HEART* Nadruz Jr and colleagues present a single centre retrospective cohort study comparing 75 patients with HF secondary to cancer treatment with 894 other HF patients.(REF) They performed a detailed evaluation with advanced echocardiography, cardiopulmonary exercise testing and report the clinical outcomes (overall survival, CV mortality, LVAD and transplantation). Eighty-nine percent of the cancer survivor HF cohort has received anthracycline chemotherapy and 44% had received radiation to the chest. The cohort with HF secondary to cancer treatment were younger with fewer cardiac co-morbidities, worse LV diastolic function, similar CPEX performance but worse clinical outcomes. Specifically mortality in the cohort of patients with HF secondary to cancer treatment with 2.64 fold higher than the comparator cohort.

When considering the importance of this finding, several factors regarding this study should be considered. It was a single centre study from a leading tertiary university hospital which may have a more advanced and complex HF population, and thus and may not reflect outcomes in community heart failure populations. The HF cohort studied was selected based on referral for CPEX testing for heart failure or cardiomyopathy, which may have also selected more advanced symptomatic HF patients being considered for possible LVAD or transplantation where CPEX testing is routine, and potential include fewer patients with HF and preserved or mid range ejection fraction (HFpEF and HFmrEF) and therefore may not reflect an unselected population of HF patients. The comparator arm were the pooled non-chemotherapy heart failure cases. This will be a heterogeneous cohort with various aetiologies and potential for variable prognosis e.g. post myocardial infarction, genetic cardiomyopathies, inflammatory cardiomyopathies.

Another important factor is the long time interval between the cancer treatment and subsequent presentation with heart failure symptoms (mean 10 years) and assessment at study enrolment (mean 18 years post chemotherapy). Firstly this is a more resistant and refractory HF cohort when the clinical presentation is late after chemotherapy, and myocardial injury is more likely to be permanent. In addition the 8 year interval between HF diagnosis and detailed assessment implies this HF cohort have a more refractory HF syndrome, as cases which have responded and reverse remodelled with evidence-based medical HF therapy may have been excluded. In the cohort with HF secondary to cancer therapy with HFrEF the rate of guideline-based HF medical therapy and ICD prevalence also appeared less. This HF cohort may also have been treated in the era before sacubitril/valsartan and ivabradine were routinely available for HFrEF patients in the US.

The study of Nadruz Jr and colleagues reinforces the view that patients who present late after anthracycline chemotherapy and/or chest radiation have a particularly severe heart failure phenotype and worse prognosis and as a medical community we should increase our efforts to prevent cardiotoxicity where possible, and to consider surveillance or screening strategies to detect cancer-therapy-associated LV dysfunction at an earlier stage, before patients present with more advanced heart failure. How can this be achieved? Prevention rather than rescue should be our

ultimate goal. This can be potentially achieved via a variety of different and complimentary approaches.

Firstly baseline cardiovascular risk assessment will identify individuals with pre-existing CV disease or multiple CV risk factors who are at higher risk of anthracycline cardiotoxicity. This should include a resting echocardiogram and measurement of troponin and natriuretic peptides to assess cardiac function at baseline pre chemotherapy. Optimising pre-existing CV disease and risk factors may help to reduced risk. Secondly cardiac surveillance during anthracycline-containing chemotherapy, particularly in higher risk patients, may detect earlier subclinical levels of cardiac injury or dysfunction and allow initiation of drugs including ACE inhibitors and beta blockers which can reduce cardiac dysfunction in higher risk patients. Surveillance using cardiac troponin and advanced echocardiography with speckle tracking to detect early reductions in left ventricular global longitudinal strain (GLS) can detect patients at risk for future left ventricular dysfunction. There is already evidence that oncology patients with troponin rises $>100\text{ng/L}$ during anthracycline chemotherapy benefit from starting enalapril,(6) and this troponin-guided ACE inhibitor strategy still proved an effective strategy compared to routine primary prevention for all patients in the recent ICOS-ONE trial.(7) We await the results of the Cardiac Care (EudraCT 2017-000896-99) and SUCCOUR (ACTRN12614000341628) trials which are assessing high sensitivity troponin elevation and speckle tracking respectively to guide initiation of cardiac treatment.

Thirdly there are other options to reduced anthracycline cardiotoxicity in selected 'high risk' cases, including dose reduction (e.g. miniCHOP for elderly lymphoma patients), choice of liposomal doxorubicin, primary prevention with dexrazoxane or ACE inhibitors and beta blockers, and use of non-anthracycline containing chemotherapy regimens when the cardiac risk is too high.

Fourthly is the introduction of routine cardiac surveillance following completion of cancer treatment in the survivor population who have received anthracycline chemotherapy or radiation to the heart. This is already established for paediatric cancer survivors who represent a particularly high risk cohort, with lifelong surveillance recommended for individuals cured of their cancer who have been treated with total cumulative doses of doxorubicin $\geq 250\text{ mg/m}^2$ or radiation to the heart of $\geq 35\text{ Gy}$, or lower doses of both given the synergistic cardiotoxic effects when combined.(8) In adults who have been treated with anthracycline chemotherapy, where the overall rate of cardiotoxicity is 9%, defined by LVEF reduction $>10\%$ and to $<50\%$, over 95% of cases can be detected during the first 12 months after completion of chemotherapy.(9) Therefore a follow up with clinical assessment, an echocardiogram and cardiac biomarkers where available at 12 months following anthracycline chemotherapy may be suitable. Beyond 12 months data on routine follow up in adult cancer survivors is not available, but many studies highlight that the problem of late cardiovascular toxicity exists, and this study confirms there is an unmet need. Surveillance could be for all patients, or targeted at those with higher risk, analogous to the paediatric survivor guidelines. However there is a further factor which requires consideration. Higher risk individuals, such as the older patients (>65 years) and those with pre-existing CV disease, the rate of clinical cardiovascular events is high in the short-medium term e.g. at 5 years post treatment. Conversely younger cancer patients, whose risk factor profile is lower, have a modest 5 year risk but their long term risk is still substantially higher than age-matched peers who did not receive cancer treatment. Therefore efforts to identify those survivors at risk is also required, including the potential to invite survivors for screening 10, 15 or 20 years following cancer treatment. The results from this cohort study of Nadruz Jr emphasises that

patients continue present with HF many years after chemotherapy or radiation therapy to the heart, and contacting cancer survivors who have been exposed to these cardiotoxic treatments should be considered to detect problems earlier.

Specialised cardio-oncology services now exist in many hospitals to deliver these services and potential solutions. Coordination between secondary and tertiary care, and between oncology, haematology and cardio-oncology services and implementation of baseline risk stratification, primary prevention, appropriate surveillance during and after chemotherapy should have an impact on this potentially serious adverse consequence of curative cancer treatment. Education of survivors to recognise cardiac symptoms and seek medical attention, and education of primary care physicians to consider cardiac late effects in cancer survivors are also important. More research trials are required to identify who is at risk before, during and at follow up after treatment, the best modalities for surveillance (biomarkers, cardiac imaging or both) and the appropriate timing and treatment intervention. As we proceed through the 21st century we need to adapt and respond to new populations of patients and medical challenges which did not previously exist, and hopefully implementation of new surveillance strategies during and after cardiotoxic cancer treatments may alter the clinical course to allow cancer survivors to live longer free of cardiovascular disease.

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