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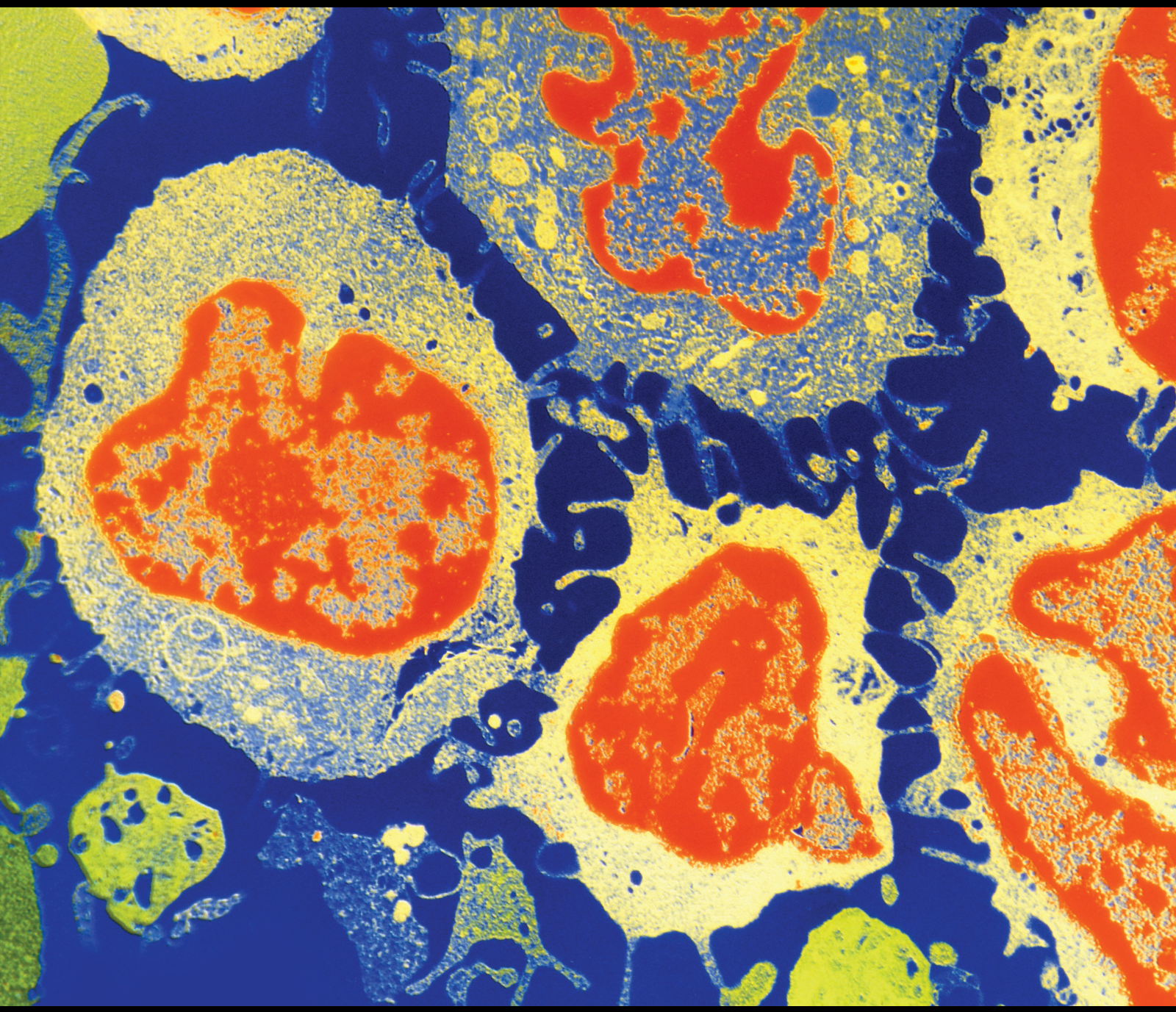
Cancer and Cardiovascular Disease: The Complex Labyrinth

Guest Editors: Susan Dent, Peter Liu, Christine Brezden-Masley, and Daniel Lenihan



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Editorial Board

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Editorial

Cancer and Cardiovascular Disease: The Complex Labyrinth

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As our population ages, there has been an increase in the prevalence of cancer and heart disease [1]. Modern treatment strategies have led to improvement in the chances of surviving a diagnosis of cancer; however, these treatments can come at a cost [2]. Cardiotoxicity, a relatively new term in the medical literature, refers to the impact of cancer therapies on the heart and cardiovascular system [3, 4]. Cohort studies in pediatric cancer survivors have shown that cardiotoxicity is the second leading cause (after cancer recurrence) of morbidity and mortality in cancer survivors [5]. The potential negative impact of cancer drugs on the heart, however, is not new. In fact, we have known for years that cancer drugs, such as the anthracyclines, can cause severe and permanent heart damage including heart failure (HF). So why is there growing interest now?

In 2005 trastuzumab in combination with chemotherapy was shown to significantly improve disease-free and overall survival in women with early stage HER2 positive breast cancer [6, 7]. While the dramatic improvements in clinical outcomes led to the widespread adoption of this treatment in clinical practice, it became readily apparent that women were experiencing higher rates of cardiac dysfunction than had been anticipated during clinical development—thus placing oncologists in a difficult situation—to treat or not to treat [8]!

The last several years have seen the development and approval of a plethora of cancer drugs, many of which may negatively impact the heart and cardiovascular system. Tyrosine kinase inhibitors (e.g., sunitinib) can cause or exacerbate preexisting hypertension and BCR-ABL inhibitors (e.g., dasatinib) can cause Q-T prolongation. In the modern era of cancer therapy it is imperative that oncologists work closely with cardiologists in order to provide the best possible cancer care without compromising cardiac health [9]. This is particularly important for those patients with preexisting heart disease who then develop cancer and are exposed to potentially cardiotoxic cancer drugs.

In this special issue we gain insight into the challenges that health care providers face when treating this unique population of patients. While our understanding of how modern cancer therapies impact the heart continues to evolve, many knowledge gaps persist.

How do we identify cancer patients at high risk of cardiotoxicity? In this issue, M. Davis and colleagues highlight the importance of cardiovascular risk assessment in cancer patients prior to commencing therapy. In a cohort of prostate cancer patients, they identified a high prevalence of baseline cardiovascular risk factors and cardiovascular disease (25%) prior to initiation of cancer therapy. A standardized approach of cardiovascular risk assessment prior to initiation of treatment is needed for all cancer patients in order to optimize cardiovascular health prior to, during, and after treatment.

What are the best modalities to detect cardiotoxicity? Two-dimensional (2D) echocardiography and MUGA scans are the most widely used modalities for monitoring cardiac function in chemotherapy treated patients—but is this the best strategy? F. Pizzino and colleagues discuss newer imaging modalities, including 2DE tissue Doppler imaging (TDI), cardiac magnetic resonance imaging (CMR), and 2D and 3D speckle tracking echocardiography. Left ventricular ejection fraction (LVEF) has been the "gold standard" used to detect

cardiotoxicity—but it is clear that this is not the best method [10]. A. Calleja and colleagues evaluated right ventricular (RV) function in breast cancer patients receiving trastuzumab (+/−anthracyclines) who had left ventricular defined cardiotoxicity. Patients with RV dysfunction at the time of LV-related cardiotoxicity had reduced recovery of LVEF although this was not statistically significant. Further research is clearly needed to determine which imaging modalities will provide the most accurate and reproducible information to detect "early" cardiotoxicity and what parameters we should be measuring in order to facilitate early intervention strategies.

How do we manage cardiotoxicity in this patient population? In this issue, J. Sulpher and colleagues clearly identify knowledge gaps between cardiologists and oncologists in the appropriate clinical management of cancer patients who develop cardiotoxicity secondary to their cancer treatment, underscoring the need for collaboration between oncologists and cardiologists. In order to facilitate this collaboration, a number of dedicated cardiac oncology clinics have been established (mainly in academic centers) but are these specialized clinics impacting patient care? J. Sulpher and colleagues describe the clinical outcomes of cancer patients referred to a dedicated cardiac oncology clinic. While their conclusions are limited by the observational nature of their study, their results are encouraging (majority of cancer patients completed treatment) and support ongoing collaboration and research in this area.

And finally how do we manage those patients who develop end stage heart disease due to cancer therapy? N. Ghosh and colleagues describe the unique challenges and clinical outcomes of cancer patients with end stage heart failure who require advanced therapies such as inotropic support, orthotopic heart transplantation, or left ventricular assist devices.

Modern cancer therapies have led to more individuals surviving a diagnosis of cancer. There is an increasing appreciation, by health care providers, of the potential negative impact of cancer therapies on cardiovascular health. This special issue adds to our current knowledge in the discipline of cardiac oncology and we look forward to future research that will help guide best practices.

Susan Dent
Peter Liu
Christine Brezden-Masley
Daniel Lenihan

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Research Article

Right Ventricular Dysfunction in Patients Experiencing Cardiotoxicity during Breast Cancer Therapy

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Background. Right ventricular (RV) dysfunction during cancer therapy related cardiotoxicity and its prognostic implications have not been examined. *Aim*. We sought to determine the incidence and prognostic value of RV dysfunction at time of LV defined cardiotoxicity. *Methods*. We retrospectively identified 30 HER2+ female patients with breast cancer treated with trastuzumab (± anthracycline) who developed cardiotoxicity and had a diagnostic quality transthoracic echocardiography. LV ejection fraction (LVEF), RV fractional area change (RV FAC), and peak systolic longitudinal strain (for both LV and RV) were measured on echocardiograms at the time of cardiotoxicity and during follow-up. Thirty age balanced precancer therapy and HER2+ breast cancer patients were used as controls. *Results*. In the 30 patients with cardiotoxicity (mean ± SD age 54 ± 12 years) RV FAC was significantly lower (42 ± 7 versus 47 ± 6%, $P = 0.01$) compared to controls. RV dysfunction defined by global longitudinal strain (GLS < −20.3%) was seen in 40% ($n = 12$). During follow-up in 16 out of 30 patients (23 ± 15 months), there was persistent LV dysfunction (EF < 55%) in 69% ($n = 11$). Concomitant RV dysfunction at the time of LV cardiotoxicity was associated with reduced recovery of LVEF during follow-up although this was not statistically significant. *Conclusion*. RV dysfunction at the time of LV cardiotoxicity is frequent in patients with breast cancer receiving trastuzumab therapy. Despite appropriate management, LV dysfunction persisted in the majority at follow-up. The prognostic value of RV dysfunction at the time of cardiotoxicity warrants further investigation.

1. Introduction

Breast cancer is the leading cause of cancer in women worldwide [1, 2]. Survival from breast cancer has improved significantly over the past 15–20 years primarily due to advances in cancer treatment [3]. However, many anticancer drugs used for the treatment of patients with breast cancer have the potential to cause cardiac toxicity (cardiotoxicity). Anthracycline-based chemotherapy and trastuzumab (TZM), a monoclonal antibody against the HER2 receptor, are of particular concern due to the high incidence of cardiotoxicity individually and with combined use [4, 5]. Once left ventricular (LV) dysfunction or heart failure (HF) occurs from anthracycline and/or TZM based therapy the prognosis can be poor with lack of LV function recovery in up to 40–58% of the patients and subsequent major adverse cardiac events [6, 7]. Due to the poor prognosis of advanced cardiac dysfunction [6, 8], many argue for efforts to identify early

cardiac dysfunction so that appropriate intervention can be initiated to prevent HF [9]. This can include administration of cardiac treatment such as beta-blockers, ACE inhibitors, and dexrazoxane; selection of alternative cancer regimens or dose adjustment; and transient cessation of cancer treatment [9]. In TZM treated patients in particular, early cardiac dysfunction is identified by repeated cardiac imaging performed prior and during cancer therapy. Cardiotoxicity is commonly defined based on a symptomatic fall in LVEF of >5 percentage points or an asymptomatic fall of >10 percentage points to <55% between pre- and during treatment measurements as defined by the cardiac review and evaluation committee criteria (CREC) [10].

To date, there has been very little focus on the toxic effects of cancer therapy on the right ventricle (RV) [11, 12]. Given the thinner structure of the RV with fewer myofibrils, the RV may also be susceptible to damage by cardiotoxic therapy. Several studies have shown that RV wall motion abnormalities [13] or functional abnormalities [12, 14] occur *during cancer therapy*; however, this finding has not been universally observed [11, 15]. The presence of RV dysfunction at the *time of LV cardiotoxicity* and whether it has prognostic implications has not been examined. However, in many other cardiovascular diseases the concomitant RV dysfunction is associated with worse outcomes [16–18]. In this study we sought to determine the incidence of RV dysfunction at the time of cardiotoxicity in women with HER2+ breast cancer receiving treatment with trastuzumab using measurements of fractional area change and myocardial peak systolic longitudinal strain. Secondly as a hypothesis generating objective we examined the prognostic value of RV dysfunction in subsequent LV function recovery during follow-up in a subgroup of patients who had follow-up imaging after completion of cancer therapy.

2. Methods

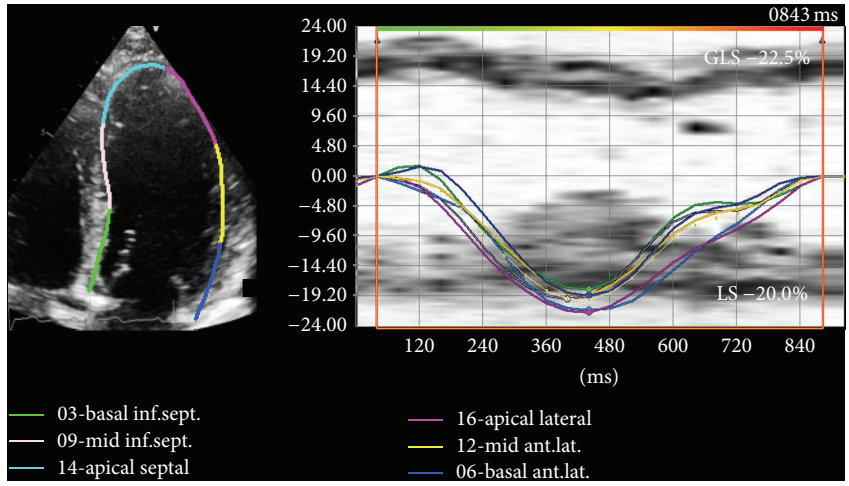
2.1. Study Population. We retrospectively identified all women >18 years of age with HER2/neu overexpressing (HER2+) breast cancer of any stage treated with TZM with or without anthracyclines at a large cancer referral center (Princess Margaret Cancer Center, Toronto, Canada) between 2006 and 2013 from the hospital pharmacy database. We included patients who (1) developed cardiotoxicity during the treatment course using the CREC criteria [10] and (2) had an echocardiogram with adequate image quality at the time of diagnosis of cardiotoxicity. For each patient the following data were obtained through electronic patient records: patient demographics, cardiac risk factors, previous cardiac history, cardiac medication use, cancer history, cancer therapy with doses used, radiotherapy history, LVEF and RVEF measurements by multigated acquisition (MUGA) pre-cancer therapy and at the time of cardiotoxicity, clinical symptoms of heart failure, and management of cardiotoxicity. The study protocol was approved by the institutional Research Ethics Board.

2.2. Controls. Age and cardiac risk factor balanced women with a diagnosis of HER2+ breast cancer without history of any previous cardiovascular disease and who had an echocardiogram prior to initiation of any cancer therapy were included as controls. This was necessary as currently existing normal values for some of the myocardial function measures used in this study such as RV strain are variable and age- and vendor-specific and have never been studied in patients with cancer. Also during the study period it was routine for patients at our center to be followed by MUGA scans as opposed to echocardiography. Therefore, since baseline echocardiography was not available in our patients with cardiotoxicity this comparison with a control group was essential.

2.3. Transthoracic Echocardiogram: Conventional Parameters and Myocardial Strain. Echocardiography studies from patients at the time of LV cardiotoxicity and from the control group were read together blinded to the group designation and clinical history. LVEF was calculated using the Biplane Simpson's method and RV FAC (analogous to LVEF) following existing American Society of Echocardiography (ASE) guidelines [19, 20].

Myocardial peak systolic longitudinal strain was measured offline for both the LV and RV based on the ASE recommendations [21] using commercially available software (Vector Velocity Imaging (VVI) 3.0, Siemens Medical Solutions, Mountain View, CA) using the speckle tracking technique. Briefly, apical 4-, 3-, and 2-chamber images of the LV and an apical 4-chamber view of the RV in DICOM format were obtained for each patient and loaded into the VVI software. Endocardial contours were drawn along the LV and RV border separately for measurement of respective longitudinal strain values (Figures 1 and 2). The contours were adjusted as needed to ensure adequate visual tracking of the endocardium. Any segments that were not tracked adequately after 5 attempts at adjustment were excluded from the analysis. LV peak systolic global longitudinal endocardial strain (GLS) was measured by taking the average of the peak endocardial strain curves in the apical 4-, 3-, and 2-chamber views (16-segment model) (Figure 1). As conventionally done, RV peak systolic global longitudinal endocardial strain (RVGLS) was measured from all 6 RV myocardial segments from an apical 4-chamber view (3 segments of the free wall and 3 segments of the interventricular septum) while the RV free wall peak systolic longitudinal strain (RVFWLS) was obtained from the 3 RV free wall segments only (Figure 2). This distinction is made since measurement of RVGLS based on the inclusion of the interventricular septum may partially reflect changes in the left ventricle as the septum is shared by both ventricles. RVFWLS focuses only on the RV free wall and does not include contribution of the septum; however, it does not account for potential changes that may occur in the RV septum.

2.4. Follow-Up. As a hypothesis generating objective, to examine the prognostic value of RV dysfunction on subsequent LV function recovery after completion of all cancer therapy, we identified those who had at least one follow-up echocardiogram ≥3 months after completion of their cancer therapy with adequate image quality. In these patients the last



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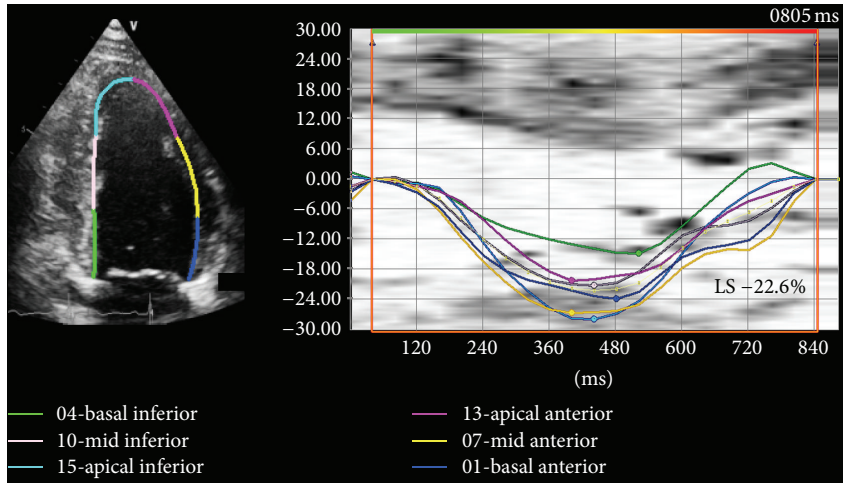

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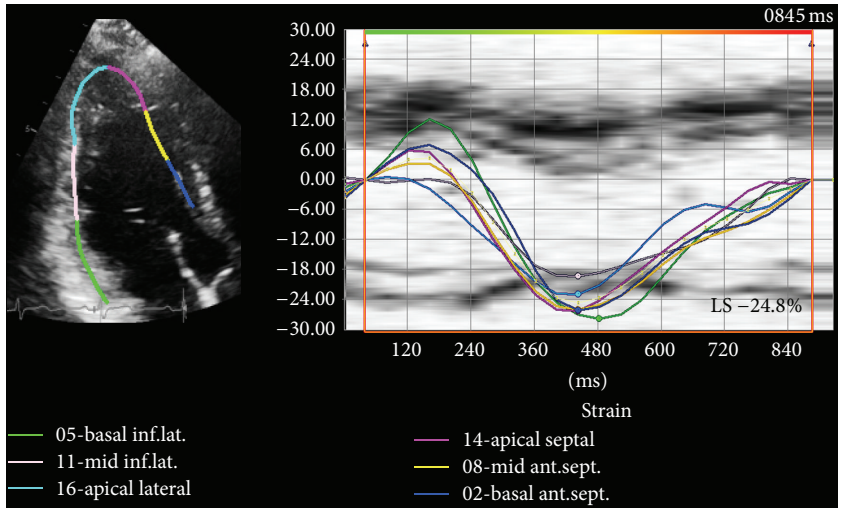

(c)

Figure 1: Left ventricular peak systolic longitudinal strain. Representative example of normal left ventricular peak endocardial strain curves: left panel shows B-mode images with endocardial tracings in the (a) 4-chamber, (b) 2-chamber, and (c) 3-chamber views with their corresponding longitudinal strain curves to its right. For each view 5-6 curves are shown representing strain values for each of the myocardial segments. Peak global longitudinal strain (GLS) is an average of the longitudinal strain (LS) values obtained from each view and a total of 16 segments (6 basal, 6 midventricular, and 4 apical segments).

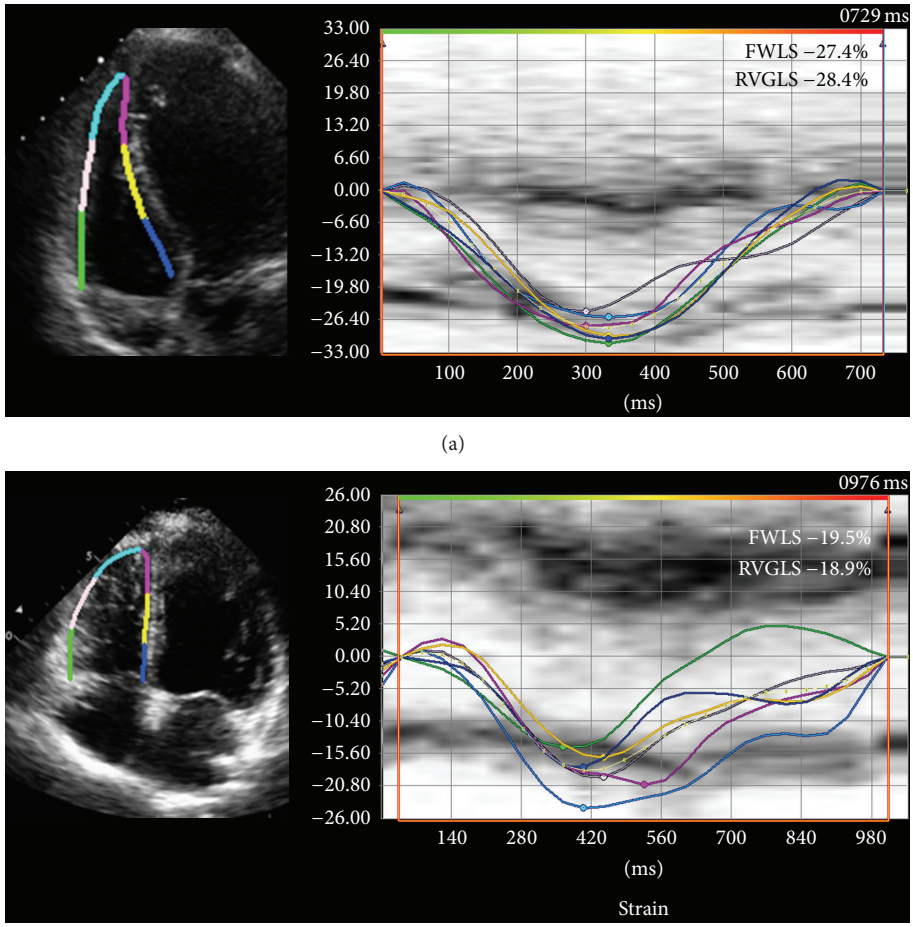

Figure 2: Right ventricular systolic longitudinal strain. Right ventricular peak endocardial strain curves. Left panel shows B-mode images of the RV in 4-chamber view with endocardial tracing and to its right is the corresponding strain curve in (a) control and (b) during cardiotoxicity. Right ventricular free wall longitudinal strain (RVFWLS) is composed of 3 segments while right ventricular peak systolic global longitudinal strain (RVGLS) includes all 6 segments (RV free wall and septum).

available echocardiogram was used to measure LVEF, FAC, and strain values. In addition the following clinical history was obtained through EPR: cardiac symptoms, medication use, and new diagnosis of other cardiac conditions.

2.5. Interobserver and Intraobserver Variability. Twenty randomly selected studies were reanalyzed by the same observer (AC) several months after the initial analysis and a second observer (FP) blinded to the original measurements for the assessment of intra- and interobserver variability of RV strain measurements.

2.6. Statistical Analysis. Normality for each variable was tested using a combination of quantile-quantile plots and the Kolmogorov-Smirnov test. Depending on the normality, variables are expressed as mean ± SD or median and interquartile range (IQR). Independent sample t-test or Wilcoxon rank sum test was used to compare continuous data between groups. A paired t-test or a Wilcoxon sign rank test was used to compare patients at the time of cardiotoxicity and at follow-up. Fisher's exact test was used to compare categorical data between the groups. Intraclass correlation coefficient (ICC) was used to assess interobserver and intraobserver variability. A P value of <0.05 was considered statistically significant. All statistical analyses were performed using MedCalc software (ver 11.4.2 Belgium).

3. Results

3.1. Patients and Cancer Treatment. A total of 598 female patients with breast cancer received trastuzumab treatment between 2006 and 2013 at the Princess Margaret Cancer Center. Amongst these patients 30 (5%) were identified as having experienced cardiotoxicity, had a diagnostic quality echocardiogram at the time of cardiotoxicity, and met our inclusion criteria. The remaining 568 patients were either not identified as having cardiotoxicity by the treating oncologist, had an echocardiography study with poor image quality at the time of cardiotoxicity, or were only followed by MUGA studies. Amongst the 30 included patients, 26 (87%) had early stage breast cancer (≤ stage III) and 4 patients had

Table 1: Patient and control demographics.

	Control $n = 30$	Cohort $n = 30$
Age	51 ± 8	54 ± 12
Stages (I–III)	30 (100%)	26 (87%)
NYHA II-III	—	16 (53%)
Cardiac risk factor		
Coronary artery disease	—	—
Hypertension	5 (17%)	6 (20%)
Diabetes mellitus	1 (3%)	3 (10%)
Dyslipidemia	—	3 (10%)
Smoker	3 (10%)	1 (3%)
Chemotherapeutic regimen		
AC-TH		13 (43%)
Epirubicin mg/m^2	—	*302.4 ± 10
FEC + DH		9 (30%)
Doxorubicin mg/m^2	—	*231.2 ± 18.7
TCH		3 (10%)
TH		5 (17%)
Radiation		23 (77%)
Mastectomy		21 (70%)
Previous cancer†		6 (20%)
Ventricular systolic function by MUGA (%)		
LVEF		
Prechemo	—	62 ± 5
At time of cardiotoxicity		48 ± 4
RVEF		
Prechemo		45 ± 4
At time of cardiotoxicity		43 ± 6

*Mean cumulative dose, †4 were previously diagnosed with breast tumor and at the time of the study were being treated for recurrence, and 2 had previous history of Ewing's Sarcoma and Hodgkin's lymphoma. AC-TH: doxorubicin and cyclophosphamide followed by either paclitaxel or docetaxel and trastuzumab; FEC-DH: 5-fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel and trastuzumab; TCH: docetaxel, carboplatin or cyclophosphamide, and trastuzumab; TH: trastuzumab and docetaxel or paclitaxel.

metastatic disease. In patients with early stage disease, 13 received doxorubicin and cyclophosphamide followed by either paclitaxel or docetaxel and TZM (AC-TH) while 9 received 5-fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel and TZM (FEC-DH), and 3 patients received docetaxel, carboplatin or cyclophosphamide, and TZM (TCH). One patient with early stage disease with history of prior early breast cancer treated with FEC twelve years before her new breast cancer diagnosis received only TZM and docetaxel. The 4 patients with metastatic disease received a combination of a taxane (either paclitaxel or docetaxel) and TZM. In patients who received anthracyclines, the mean cumulative dose of epirubicin administered was 302 ± 10 mg/m^2 while in those who received doxorubicin the mean dose was 231 ± 19 mg/m^2 (Table 1).

Table 2: Conventional and strain parameters measured by echocardiography in patients with cardiotoxicity and the control group.

	Control $n = 30$	Cardiotoxicity $n = 30$	P
Left ventricle			
EF Biplane (%)	59 ± 2	46 ± 6	<0.0001
GLS	−21.1 ± 1.2	−15.5 ± 2.4	<0.0001
Right ventricle			
RVSP mmHg	24 ± 6.4	29 ± 7.5	0.01
FAC (%)	47 ± 6	42 ± 7	0.01
RVFWLS	−28.8 ± 3.6	−25.0 ± 4.3	0.0005
RVGLS	−25.7 ± 2.7	−21.0 ± 3.1	<0.0001

GLS: global longitudinal strain, FAC: fractional area change, RVFWLS: right ventricular free wall longitudinal strain (3 segments), and RVGLS: right ventricular global longitudinal strain (includes all 6 segments).

3.2. Timing and Management of Cardiotoxicity. All patients with cardiotoxicity had normal pre-chemotherapy LV and RV function by MUGA with a mean LVEF of 62 ± 5% and mean RVEF of 45 ± 5%. In patients who received anthracycline followed by trastuzumab ($n = 22$), cardiotoxicity occurred immediately after anthracycline therapy in one and during trastuzumab treatment in the rest with a median (IQR) time to occurrence of 5.0 (5.0) months. In the 8 patients who received trastuzumab without anthracyclines, the median (IQR) time to cardiotoxicity was 7.5 months (5.7). At the time of cardiotoxicity, 17 (57%) patients reported symptoms consistent with NYHA 2-3, while the rest were NYHA 1. Management of cardiotoxicity included withholding TZM treatment only in 10 patients, adding ACE inhibitors and/or beta-blockers along with withholding TZM in 9 patients, and starting ACE inhibitors and/or beta blockers while continuing TZM in 4. In 7 patients, TZM was continued with close monitoring. The latter reflects the variability in clinical practice.

3.3. Ventricular Function at Time of Cardiotoxicity. LV function by MUGA was significantly reduced to 48 ± 4% compared to pretreatment values of 62 ± 5% ($P < 0.0001$). LVEF by MUGA and echo at the time of cardiotoxicity were not significantly different (48 ± 4% versus 46 ± 6%, $P = 0.13$). When compared to controls, the LVEF by echocardiography in patients with cardiotoxicity was significantly lower as expected (59 ± 2% versus 46 ± 6, $P < 0.0001$). Similarly LV peak systolic global longitudinal strain (GLS −21.1 ± 1.2% versus −15.5 ± 2.4%, $P < 0.0001$) was significantly lower in patients with cardiotoxicity compared to controls (Table 2). This value is also significantly lower than the published lower limit of normal for LV GLS of −18.9% ($P < 0.001$) [9, 22].

Precancer treatment RV function by MUGA was 45 ± 4% (normal) [23] while at the time of cardiotoxicity it was 43 ± 6 ($P = 0.19$). None of the patients had abnormal RV function pretherapy. By echocardiography at the time of cardiotoxicity the mean RV function by FAC was significantly lower than the controls although still in the normal range (42 ± 7% versus 47 ± 6% $P = 0.01$) with 3 (10%) patients having

Table 3: Ventricular function at the time of cardiotoxicity by chemotherapy agent received.

	(+) Anthracycline $n = 22$	(−) Anthracycline $n = 8$
Time to toxicity in months*	5 (5)	7.5 (5.7)
Left ventricle		
Baseline EF by MUGA (%)	62 ± 6	60 ± 3
Cardiotoxicity EF by MUGA (%)	48 ± 4	47 ± 4
Cardiotoxicity EF by ECHO (%)	46 ± 6	44 ± 5
Cardiotoxicity GLS	−15.5 ± 2.5	−15.7 ± 2.5
Right ventricle		
Baseline EF by MUGA (%)	46 ± 4	43 ± 3
Cardiotoxicity EF by MUGA (%)	44 ± 6	40 ± 5
Cardiotoxicity FAC by ECHO (%)	42 ± 8	43 ± 5
Cardiotoxicity RVFWLS	−24.1 ± 3.9	−27.4 ± 4.6
Cardiotoxicity RVGLS	−20.4 ± 2.8	−22.8 ± 3.2

*Median (IQR) onset of cardiotoxicity which occurred after initiation of TZM therapy in 21 patients; in 1 patient toxicity occurred after 3 months from the start of chemotherapy. Abbreviations as per Table 2.

Table 4: Ventricular function at time of cardiotoxicity and at follow-up ($n = 16$) in patients with only left ventricular dysfunction at the time of cardiotoxicity and in those with biventricular dysfunction.

	Cardiotoxicity	Posttreatment
Left ventricular dysfunction $n = 10$		
EF Biplane (%)	44 ± 7	51 ± 9
GLS	−15.7 ± 2.4	−17.6 ± 3.1
FAC (%)	44 ± 5	46 ± 9
RVGLS	−22.2 ± 1.4	−23.2 ± −5.5
RVFWLS	−27.0 ± 3.2	−26.1 ± 6.6
Biventricular dysfunction based on RVGLS $n = 6$		
EF biplane (%)	47 ± 3	52 ± 3
LV GLS	−14.4 ± 1.7	−16.4 ± 1.6
FAC	39 ± 11	48 ± 6
RVGLS	−17.8 ± 1.2	−22.3 ± 2.9
RVFWLS	−21.6 ± 2.8	−26.3 ± 5.0
Biventricular dysfunction based on RVFWLS $n = 3$		
EF biplane (%)	49 ± 5	52 ± 2.5
LV GLS	−15.6 ± 0.8	−16.1 ± 1.1
FAC	33 ± 11	48 ± 3
RVGLS	−14.6 ± 0.7	−21.8 ± 2.1
RVFWLS	−19.5 ± 1.1	−23.5 ± 2.4

Abbreviations as per Table 2.

an abnormal FAC (<35%). The RV strain was significantly decreased (*i.e., less negative*) in patients with cardiotoxicity compared to controls for both RVGLS (−21.0 ± 3.1% versus −25.7 ± 2.7%, $P < 0.0001$) and RVFWLS (−25.0 ± 4.3% versus −28.8 ± 3.6%, $P = 0.005$) (Table 2). Using a cut-off value of −20.3% for RVGLS and −21.6% for RVFWLS (2SD below mean value for the controls), 12 (40%) and 5 patients (17%), respectively, had reduced RV function by strain analysis. The RVSP (a marker of pulmonary systolic pressures) was also slightly higher in patients with cardiotoxicity compared to controls (Table 2) although still within the normal range. The changes in LV and RV parameters at the time of cardiotoxicity in patients who received anthracycline versus those who did not are summarized in Table 3.

3.4. Ventricular Function at Follow-Up. Follow-up echocardiograms at least *3 months after completion of cancer therapy* were available in 16 of the 30 patients. Mean time from completion of therapy to follow-up echocardiogram was 23 ± 15 months. At follow-up, compared to the time of cardiotoxicity, there was significant improvement in LVEF (from 45 ± 6% to 52 ± 7%, $P = 0.0001$) and LV GLS (−15.2 ± 2.2 to −17.2 ± 2.6%, $P = 0.004$). However, only 5 patients at follow-up had a Biplane LVEF in the normal range (i.e., ≥55%). The mean RV function measured by FAC did not change significantly between the time of cardiotoxicity and follow-up (43 ± 8% to 46 ± 8%, $P = 0.13$). Likewise there was no significant improvement in RVGLS (−20.5 ± 2.6% to −22.9 ± 5% $P = 0.09$) or RVFWLS (−25.0 ± 3.9% to −26.2 ± 5.9% $P = 0.48$) at follow-up. The changes in LV and RV parameters between time of cardiotoxicity and follow-up in patients with LV dysfunction only versus those with coexisting LV and RV dysfunction at the time of cardiotoxicity is summarized in Table 4. Also ventricular function parameters at baseline, at the time of cardiotoxicity, and at follow-up are provided separately for patients with and without LVEF recovery in Table 5.

We also examined the association between RV strain abnormalities at the time of cardiotoxicity and subsequent recovery of LVEF at follow-up. LVEF recovery was seen in only 1 out of 6 patients (17%) with abnormal RVGLS at the time of cardiotoxicity while it was seen in 4 out of 10 patients (40%) with normal RVGLS ($P = 0.59$). Similarly, recovery in LVEF did not occur in any of the 3 patients (0%) with abnormal RVFWLS at the time of cardiotoxicity while it occurred 5 out of 13 patients (38%) with normal RVFWLS ($P = 0.51$). When patients with and without LV function recovery were compared, none of the patients with ventricular function recovery had any cardiac risk factors (diabetes, hypertension, or hypercholesterolemia) while 64% of the patients without recovery had at least 1 cardiac risk factors. There was no difference in mean age (57 ± 24 years

Table 5: Ventricular function parameters at the time of cardiotoxicity and at follow-up ($n = 16$) in patients with and without left ventricular ejection fraction recovery to ≥55%.

	(+) LV recovery $n = 5$	(−) LV recovery $n = 11$
Left ventricle		
Baseline EF by MUGA (%)	62 ± 8	61 ± 4
Cardiotoxicity EF by MUGA (%)	49 ± 3	45 ± 3
Cardiotoxicity EF by ECHO (%)	49 ± 6	44 ± 6
Post-treatment EF by ECHO (%)	59 ± 2	48 ± 6
Cardiotoxicity GLS	−15.6 ± 2.8	−15.0 ± 1.9
Post-treatment GLS	−19.8 ± 2.3	−16.0 ± 1.8
Right ventricle		
Baseline EF by MUGA (%)	48 ± 3	48 ± 4
Cardiotoxicity EF by MUGA (%)	41 ± 5	42 ± 4
Cardiotoxicity FAC by ECHO (%)	45 ± 3	42 ± 9
Post-treatment FAC by ECHO (%)	54 ± 4	43 ± 8
Cardiotoxicity RVFWLS	−25.3 ± 2.2	−24.8 ± 4.6
Post-treatment RVFWLS	−32.1 ± 5.3	−23.4 ± 3.8
Cardiotoxicity RVGLS	−21.1 ± 1.8	−20.2 ± 2.8
Post-treatment RVGLS	−24.6 ± 3.7	−22.1 ± 4.9

Abbreviations as per Table 2; recovery is defined as an LVEF ≥55% at last follow-up.

versus 56 ± 9 years, $P = 0.87$), mean duration of follow-up (26 ± 14 versus 22 ± 15 $P = 0.58$), the proportion that received anthracyclines (80% versus 73%, $P = 0.99$), and the lowest mean LVEF during cardiotoxicity (49 ± 6% versus 44 ± 6%, $P = 0.14$), between patients with and without recovery, respectively. In the 5 patients with LVEF recovery, 2 were treated with cardiac medications at 1.5 and 4 months from the diagnosis of cardiotoxicity, while in 11 patients without recovery 8 received cardiac medications, with 6 treated at mean of 1.7 ± 1.4 months from diagnosis of cardiotoxicity and 2 patients were treated after 3.5 months due to fluctuating LVEF.

In the remaining 14 out of 30 patients not described above; repeat imaging was done in 11 during the course of cancer treatment but not afterwards, 2 patients had echocardiograms early after treatment completion but were technically inadequate for strain analysis, and one patient was lost to follow up. When these 14 patients were compared to the 16 patients above, there was no statistically significant difference in age (51 ± 14 versus 58 ± 11, $P = 0.10$) or echocardiographic parameters at the time of cardiotoxicity: LVEF (46 ± 6% versus 45 ± 6% $P = 0.97$), GLS (−15.9 ± 2.7% versus −15.2 ± 2.2%, $P = 0.27$), RV FAC (42 ± 6% versus 43 ± 8%, $P = 0.57$), RVFWLS (−25.1 ± 4.8% versus −25.0 ± 3.9%, $P = 0.68$), and RVGLS (−21.6 ± 3.6% versus −20.5 ± 2.6%, $P = 0.62$). In the 13 patients, LVEF at interim follow-up was significantly higher compared to the time of cardiotoxicity (45 ± 6 versus 53 ± 12, $P = 0.02$); however only 7 patients had LVEF >55% at the last available study.

3.5. Intraobserver and Interobserver Variability. For the measurement of RVFWLS and RVGLS the intraobserver ICC were 0.97 and 0.97, respectively, while the interobserver ICC were 0.80 and 0.90, respectively.

4. Discussion

Our study demonstrates that in women with HER2+ breast cancer that experienced LV cardiotoxicity during treatment with trastuzumab (with or without anthracycline therapy), RV function at the time of cardiotoxicity is lower than controls as measured using FAC (a measure analogous to ejection fraction for the LV) and strain. RV dysfunction was seen in 10% of the patients by FAC and in up to 40% of the patients based on strain analysis by speckle tracking echocardiography. The proportion of patients with abnormal strain was larger than those with abnormal FAC demonstrating the sensitivity of strain measures to identify subtle ventricular dysfunction. In a subgroup of patients with a mean follow-up of 23 months after completion of cancer therapy, LV dysfunction persisted despite appropriate management. Finally, recovery of LV function was lower in patients who had concomitant RV dysfunction at the time of cardiotoxicity compared to those who did not (17% versus 40%); however, this did not reach statistical significance, likely reflecting our small sample size.

4.1. Right Ventricular Dysfunction and Cardiotoxicity. In women with HER2+ breast cancer receiving trastuzumab therapy alone or in combination with anthracyclines the incidence of cardiotoxicity (defined by fall in LVEF) in clinical trials has been reported to be as high as 14% [24]. However, in retrospective population based studies the rates are much higher ranging from 15.5 to 41.9% especially in older women and over long term follow-up [25, 26]. The identification of cardiotoxicity has been primarily based on development of LV systolic dysfunction and eventual HF. Currently, RV dysfunction is not considered in the diagnosis of cardiotoxicity and its incidence and prognostic value in patients receiving cancer therapy is unknown. The limited literature on the impact of cancer therapy on the RV may reflect the absence of robust techniques for the assessment of RV function. However, given the thinner structure of the RV with fewer myofibrils, the RV may also be susceptible to damage by cardiotoxic cancer therapy as we have shown in this study. In fact the recent ASE expert consensus statement on the multimodality imaging of adult patients receiving

cancer therapy recommends monitoring RV function during cancer therapy [9].

The effect of cancer therapy on the RV was first demonstrated in an older study of 41 doxorubicin treated patients with various cancers where RV wall motion abnormalities were more common than LV abnormalities on radionuclide ventriculography [13]. More recently, a cardiac MRI study of 46 women with breast cancer receiving anthracyclines with or without trastuzumab illustrated RV dysfunction in 34% of the patients by 12 months, while LV dysfunction was seen in 26% [12]. Interestingly RV dysfunction was present as early as 4 months into therapy and was felt to represent an early sign of myocardial injury. Another echocardiography study identified mild reduction in RV FAC and tricuspid annular plane systolic excursion (TAPSE) even as early as the 3rd cycle of doxorubicin therapy in 37 anthracycline treated patients with breast cancer [14]. Two other studies of 19 and 56 survivors of pediatric cancers have shown a reduction in RV free wall strain values (a marker of subclinical ventricular dysfunction) at cumulative anthracycline (various) doses $<300\ mg/m^2$ [27, 28]. In more recent study of patients with advanced HF receiving LV mechanical circulatory support, patients with chemotherapy induced cardiomyopathy were significantly more likely to also require RV mechanical support [29]. However, these findings have not been consistent amongst studies. Two small studies of patients treated with similar doxorubicin equivalent doses as above studies did not demonstrate RV dysfunction by radionuclide angiography and echocardiography when comparing pre- to posttherapy time points [11, 15]. Also, the incidence of concomitant RV dysfunction *at the time of cardiotoxicity* has not been previously studied.

Our work builds on the existing literature by demonstrating that, in women with HER2+ breast cancer receiving trastuzumab therapy, RV dysfunction is seen *at the time of cardiotoxicity*. When compared to controls, the mean FAC, RVGLS, and RVFWLS were significantly reduced in patients experiencing cardiotoxicity. In addition 10% of the patients had abnormal RV function by FAC. Similarly using a threshold for abnormal strain generated based on the control group; up to 40% of patients had abnormal RVGLS or RVFWS. The higher incidence of RV dysfunction based on strain abnormality reflects the higher sensitivity of this measure for myocardial dysfunction. Ventricular strain is a marker of myocardial deformation and has been used widely for the detection of subclinical cardiotoxicity in many diseases including patients receiving cancer therapy [30]. We demonstrate the use of these measures for the first time for the assessment of RV dysfunction *at the time cardiotoxicity* in patients treated with trastuzumab.

4.2. Recovery of Ventricular Function. Generally in trastuzumab treated patients with breast cancer, LV dysfunction that occurs at the time of cardiotoxicity is thought to recover with cessation of trastuzumab [31]. However, this finding has not been universal with some studies demonstrating lack of recovery in LV function in as many as 40% of the patients despite receiving appropriate cardiac therapy [7]. Our study demonstrates that 69% of the patients had persistently abnormal LVEF (<55%) at follow-up, and 3 (19%) remained symptomatic (NYHA $\geq$ 2). Although the incidence likely exaggerated due to incomplete follow-up, our data suggest that LV dysfunction persists in a significant proportion of patients who experience cardiotoxicity during trastuzumab therapy despite appropriate management. A recent study demonstrated that persistent LV dysfunction in follow-up in patients treated for cancer was associated with higher mortality [32]. Mortality data was not available in our study. Also, interestingly our study demonstrates that a significant proportion of patients with abnormal RV function measured by strain at the time of cardiotoxicity did not have subsequent recovery in LV function at follow-up. This suggests that concomitant RV dysfunction may be a marker of more significant cardiac injury and a potential risk factor for persistent LV dysfunction during follow-up. However, given our small sample size this difference did not reach statistical significance. These findings are hypothesis generating and will need to be confirmed in larger studies.

4.3. Limitations. This was a retrospective study from a single center with a relative small sample size. However, the low rates of cardiotoxicity at our center and the fact that cardiac function is generally followed by MUGA as opposed to echocardiography explain our small sample size. Also we did not have baseline echocardiography in our patients with cardiotoxicity to ensure that their LV and RV function were normal pre-cancer therapy and to compare strain and EF values at baseline to the time of cardiotoxicity. However, by MUGA, all of the patients had normal pre-cancer therapy LV and RV function. Furthermore, we used an age and cardiac risk factor balanced control group of HER2+ breast cancer patients who had echocardiography prior to any cancer treatment to account for this limitation. Post-cancer therapy follow-up data was only present in 53% of the patients. This reflects the retrospective nature of the study, and the fact that many patients are not routinely followed with cardiac imaging at our tertiary care center once cancer therapy is completed. Therefore our estimates of ventricular function recovery must be considered in the context of this limitation and is likely higher than expected in clinical practice. We have however shown that the 14 patients without postcancer treatment follow-up were similar to the 16 patients with follow-up with respect to clinical and echocardiographic parameters. We did not include these latter 14 in the follow-up cohort as any conclusion about ventricular function recovery is hampered by ongoing cancer treatment. We also had patients with variability in the cancer treatment. However, all patients received trastuzumab therapy with a majority (73%) also having received anthracyclines. We also did not report measures of TAPSE and systolic annular velocities as additional measures of RV function as this was not consistently available in all the patients. However, we did measure RVGLS in our patients and this has been shown to be a good marker of RV function when compared to the gold-standard of cardiac MRI [33]. Cardiac MRI is considered the reference standard for RV function assessment, but we did not have cardiac MRI data in our patients as this was not standard of care. Finally we did not do a logistic regression

analysis of predictors of LV recovery as the number of events was small to meaningfully adjust for confounders.

4.4. Clinical Implication. The finding of RV dysfunction during the diagnosis of cardiotoxicity in our study demonstrates the need to assess both ventricles during cancer therapy in patients with breast cancer receiving trastuzumab therapy. This is consistent with recent guidelines from the American Society of Echocardiography, which encourages routine follow-up of both LV and RV functions during cancer treatment [9]. Also, our findings of persistent LV dysfunction during follow-up have implications for cardiac therapy in patients experiencing cardiotoxicity. The appropriate length of treatment with cardiac medications such as beta-blockers and ACE inhibitors in patients experiencing cardiotoxicity during cancer therapy is unknown. Based on our findings of persistently reduced LVEF it may be necessary to continue cardiac treatment for a prolonged period of time. In addition, these patients may need close cardiology follow-up.

5. Conclusion

In patients with HER2+ breast cancer treated with trastuzumab with or without anthracyclines who experienced cardiotoxicity (based on reduction in LVEF), concomitant RV dysfunction was seen in up to 40% of the patients based on RV strain measurements. During follow-up after completion of cancer therapy, LV dysfunction (LVEF < 55%) persisted in 69%. Patients with concomitant LV and RV dysfunction at the time of cardiotoxicity had a lower propensity for subsequent ventricular function recovery although this did not reach statistical significance. The prognostic value of RV dysfunction and its persistence during follow-up needs to be assessed in larger studies.

Conflict of Interests

None of the authors have any conflict of interests.

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Review Article

Orthotopic Heart Transplantation and Mechanical Circulatory Support in Cancer Survivors: Challenges and Outcomes

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Chemotherapy-induced cardiomyopathy (CCMP) is a significant cause of morbidity and mortality. Compared to cardiomyopathy due to other causes, anthracycline-induced cardiomyopathy is associated with a worse survival. As cancer survival improves, patients with CCMP can be expected to comprise a significant proportion of patients who may require advanced therapies such as inotropic support, cardiac transplantation, or left ventricular assist device (LVAD). Distinct outcomes related to advanced therapies for end-stage heart failure in this patient population may arise due to unique demographic characteristics and comorbidities. We review recent literature regarding the characteristics of patients who have survived cancer undergoing orthotopic heart transplantation and mechanical circulatory support for end-stage heart failure. The challenges and outcomes of advanced therapies for heart failure related specifically to anthracycline-induced cardiomyopathy are emphasized.

1. Introduction

Chemotherapy-induced cardiomyopathy (CCMP) is a significant cause of morbidity and mortality [1]. Compared to cardiomyopathy due to other causes including idiopathic cardiomyopathy and ischemic cardiomyopathy, anthracycline-induced cardiomyopathy is associated with a worse survival [2]. Up to 2–4% of patients with anthracycline-induced cardiomyopathy progress to end-stage heart failure, a proportion of who may require advanced therapies such as inotropic support, orthotopic heart transplantation (OHT), or left ventricular assist device (LVAD) [1]. As such, the feasibility of advanced therapies is an important consideration in this patient population [1].

Distinct outcomes related to advanced therapies for end-stage heart failure in this patient population may arise due to unique demographic characteristics and comorbidities. Furthermore, there are pathophysiological differences between anthracycline-induced cardiomyopathy and other causes of cardiomyopathy that may impact feasibility of isolated left ventricular support. Indeed, the mechanisms of cardiac injury after anthracycline-induced chemotherapy are significantly different from those involved in ischemic or idiopathic/dilated cardiomyopathy [3]. Anthracycline-induced cardiomyopathy is thought to be mediated by a variety of mechanisms including the production of free radicals, mitochondrial damage, and mitochondria-dependent apoptosis. Doxorubicin has also been shown to intercalate DNA by forming complexes with topoisomerase II beta. The resulting histological findings include cytoplasmic vacuolization, myofibril loss and disarray, cellular necrosis and fibrosis [4, 5]. It must be noted, however, that the diagnosis of anthracycline-induced cardiomyopathy in most studies has been presumed based on clinical history and exclusion of other causes. Right ventricular endomyocardial biopsy with the cardinal findings of anthracycline-induced cardiotoxicity is the gold standard for confirming anthracycline-induced cardiotoxicity as the cause of cardiomyopathy.

The case illustration introduces several important challenges that clinicians who are caring for patients with end-stage heart failure due to cancer treatment face. These include the implications of the oncologic prognosis on heart failure treatment options and the impact of prior cancer treatment

on perioperative and longer-term outcomes after LVAD implantation or OHT.

Important concepts related to the advanced heart failure in cancer patients have been recently reviewed [6, 7]. Shah and Nohria highlight the pathophysiology, clinical presentation, and management of heart failure due anthracyclines, targeted therapies, and restrictive cardiomyopathy secondary to thoracic radiation [6]. Importantly, the review outlines preventative strategies and pharmacological management of left ventricular dysfunction due to cancer treatment. Oliveira et al. recently critically appraised the data available for advanced therapies including implantable cardioverter defibrillator, cardiac resynchronization therapy, OHT, and mechanical circulatory support (MCS) for chemotherapy-induced cardiomyopathy [7].

This paper will specifically focus on the current knowledge of the epidemiology and outcomes related to OHT and MCS in patients with a history of cancer with a focus on patients with presumed anthracycline-induced cardiomyopathy. Herein, CCMP and anthracycline-induced cardiomyopathy will be used interchangeably.

2. Case Illustration

A fifty-seven-year-old female is admitted to hospital with symptoms of congestive heart failure including dyspnea, orthopnea, and paroxysmal dyspnea. Echocardiography shows severely globally reduced left ventricular ejection fraction (LVEF) of 10–15% with mild dilation, moderately reduced right ventricular function, moderate mitral regurgitation, and severe tricuspid regurgitation. Coronary angiography shows no evidence of coronary atherosclerosis. She undergoes further diuresis and is started on low dose ace-inhibitors and digoxin and is subsequently discharged home in stable condition.

Eleven months prior, she underwent treatment with 4 cycles of adjuvant Adriamycin/Cytoxan chemotherapy after mastectomy and radiation to the right chest for T2N3M0, estrogen receptor negative/progesterone receptor negative/HER2 negative "triple negative", breast cancer. She received a total dose of 240 mg/m^2 of Adriamycin for breast cancer. Prior to initiation of chemotherapy for breast cancer, echocardiography showed normal LVEF (>55%).

At the age of 22, she was diagnosed with non-hodgkin's lymphoma (NHL) involving the chest, abdomen, and pelvis for which she was treated with Adriamycin-based chemotherapy and partial small bowel resection. The dose of Adriamycin given during this treatment was unknown.

Three months following her initial heart failure admission, she presents again with decompensated heart failure. Right heart catheterization reveals a cardiac index of 1.4, right atrial pressure of 16 mmHg, pulmonary artery pressure of 46/22 mmHg (30), pulmonary capillary wedge pressure of 20 mmHg, and systemic vascular resistance of 2000 dyn$*$s/cm^5. Milrinone is initiated with symptomatic improvement, an increase in cardiac index to 2.1 and a decrease in systemic vascular resistance to 1065 dyn$*$s/cm^5. During this hospitalization, the Advanced Heart Disease service is consulted for consideration of advanced therapies for heart failure. To guide decision-making, the patient's cancer prognosis is discussed with the patient's Oncologist who quotes a risk of recurrence of breast cancer of >50% in the next 3 to 5 years. After careful discussion with the patient and members of her multidisciplinary clinical team, the decision is made to discharge the patient on home intravenous milrinone therapy.

The patient remains stable on home intravenous milrinone therapy for one month. However, she represents to an outside hospital with a 20 lb weight gain, abdominal bloating, orthopnea, and paroxysmal dyspnea. Intravenous dobutamine is added to her regimen. The patient is transferred to a tertiary care hospital for consideration of destination therapy LVAD. After transfer, the patient undergoes further diuresis, and with dobutamine at 2.5 mcg/kg/min and milrinone at 0.5 mcg/kg/min being administered, she undergoes right heart catheterization (RHC). RHC shows a central venous pressure of 22 mmHg, pulmonary artery pressure of 38/22 (27), pulmonary capillary wedge pressure of 25 mmHg, cardiac index of 2.5, and arterial blood pressure of 72/48 mmHg. Hemodynamics is further optimized by increasing dobutamine to 4 mcg/kg/min further diuresis, and insertion of an intra-aortic balloon pump. CVP improves to 14 mmHg and PCWP to 14 mmHg. On the same day, the patient undergoes implantation of Thoratec's HeartMate II left ventricular assist device. After LVAD implantation, she shows signs of persistent right ventricular failure including central venous pressure in the low to mid 20's mmHg despite adequate left ventricular unloading. She is taken back to the operating room for the TandemHeart right ventricular assist device. Her postoperative course is further complicated by acute kidney injury and acute respiratory distress syndrome. On postoperative day 13, she is found to be unresponsive. Computed tomography shows massive intracranial hemorrhage. The family decides to transition her care philosophy to comfort measures only. The patient dies peacefully, surrounded by her family, on postoperative day 14.

3. Orthotopic Heart Transplantation (OHT)

OHT in survivors of cancer carries the potential risk of relapse of the primary malignancy, leading to the concern for poorer prognosis after OHT. The concern for post-OHT malignancy is greater for cardiac transplantation compared to other solid organ transplants such as renal transplantation because of a relatively increased level of immunosuppression required due to less extensive HLA matching [8].

Current guidelines state that a history of active cancer in the form of a solid tumor or hematological malignancy within five years is a contraindication to heart transplantation [9]. For those who are beyond this window, recent evidence involving larger patient cohorts [10–13] suggests that outcomes for both pediatric and adult survivors of cancer who develop end-stage heart failure are comparable to recipients without a history of cancer.

In a recent study of 7169 pediatric heart transplant recipients who were identified using the UNOS (United Network for Organic Sharing) database, several important observations were made. Of the overall cohort, 1.5% had a

history of childhood cancer ($N = 107$). Of these 107 patients, 25% had a history of leukemia. The incidence of post-OHT malignancy was significantly higher in recipients with a pre-OHT history of cancer than those without (13% versus 5.4%, resp., $p < 0.001$). Despite the increased risk of posttransplant malignancy, overall survival at one year and at five years was similar in the two groups (90.6% and 80.3%, resp., in the cancer group, and 84.4% and 73.8%, resp., in the noncancer group, $p < 0.001$). Survival was also the same when only patients, with cardiomyopathy (rather than congenital heart disease) as the reason for transplantation, were compared [14].

Similar outcome patterns have been observed in adult patients with a history of cancer undergoing OHT. Oliveira et al. looked specifically at characteristics and outcomes of adult patients undergoing OHT for presumed CCMP [1]. The patient cohort was derived from the International Society of Heart and Lung Transplantation (ISHLT) Registry, from which 232 heart transplant patients aged 18 or older who carried a diagnosis of CCMP were identified. This group was compared to a control group of 8890 patients with NICM who underwent OHT during the same time period. The most common malignancies were hematologic (33%), followed by breast cancer (31%) and sarcomas (7.5%), malignancies for which anthracyclines are frequently the mainstay of therapy.

Important baseline differences were observed between the groups. First, a significantly greater proportion of the CCMP group was females compared to the NICMP group that was females (65% females in the CCMP group versus 25% females in the NICM group, $p < 0.001$). This is despite the fact that hematologic malignancies and sarcomas comprised a greater proportion of cancers (44%) compared to breast cancer (31%), raising the possibility that women may be more vulnerable to anthracycline-induced cardiomyopathy than men [1]. Interestingly, the CCMP group had a greater need for right ventricular assist device prior to transplantation compared to the NICM group, a finding that may have important implications for both the underlying pathophysiology of CCMP and the feasibility of isolated LVAD in this patient population. This will be further discussed in the section reviewing MCS below.

As observed in the pediatric study, the post-OHT malignancy rate was significantly greater in the CCMP group compared to the control group (5% in the CCMP group versus 2% in the NICMP group, $p = 0.006$) [1]. The majority of the cancers in both groups were nonfatal skin cancers with only one patient having recurrence of his pre-OHT malignancy (breast cancer). Despite these differences in post-OHT malignancy rates, post-OHT short-term and long-term survival rates were similar between the two groups. At 1 and 5 years, survival in the CCMP group was 86% and 71%, respectively. In the NICMP group, survival at 1 and 5 years was 87% and 74%, respectively [1]. Furthermore, there was no statistically significant difference in malignancy as being the cause of death in either group at 1 and 5 years.

In summary, the evidence outlined above suggests that both children and adults with CCMP prior to OHT have comparable and favorable survival compared to those with other causes of end-stage heart disease. This is despite higher rates of malignancy post-OHT. Indeed, the malignancies were rarely due to recurrence of the original malignancy. The study by Oliveira et al. also suggests that patients who undergo OHT for CCMP have a lower burden of comorbidities including renal dysfunction, hypertension, and diabetes [1].

Some outstanding questions remain. What is the underlying cause of greater rates of malignancy in patients undergoing OHT after transplantation? Does it reflect overzealous post-OHT immunosuppression or does it suggest residual intrinsic immunodeficiency after treatments with potential toxicity to the bone marrow and other immune-modulating agents? Does the lower rate of comorbidities reflect stricter selection for this patient population on the part of the treating clinicians or does it simply reflect the general profile of patients considered for transplantation?

Overall, OHT outcomes in patients with a history of cancer and probable CCMP are favorable with survival similar to other OHT recipients. Therefore, anthracycline treatment or a history of cancer should not preclude consideration of OHT particularly if the cancer has been in remission for five years or more as endorsed by current guidelines [15]. Oliveira et al. suggest that the 5-year post-remission OHT eligibility criterion should be replaced by eligibility on a case-by-case basis in consultation with the oncology team [7]. Prospective studies are required to support the safety and feasibility of this approach.

4. Mechanical Circulatory Support (MCS)

Unlike other causes of cardiomyopathy, OHT may be contraindicated due to coexistence of malignancy or timing of malignancy remission. As such, when conventional therapies for heart failure have been exhausted, MCS such as LVAD may remain the only option outside of supportive care. This section will review the current literature regarding the epidemiology, outcomes, and specific challenges associated with LVAD as both destination therapy (DT) and bridge to transplantation (BTT) in patients with CCMP.

Characteristics of Patients Undergoing LVAD Implantation. Until recently, there was a paucity of data regarding MCS in patients with end-stage heart failure due to anthracycline-induced cardiomyopathy. Several case reports describe LVAD implantation serving as a bridge to recovery of cardiac function in presumed anthracycline-induced cardiomyopathy, refuting the widely held concept that anthracycline-induced cardiomyopathy is irreversible (the so-called type I cardiotoxicity) [16–18]. LVAD as bridge to recovery is expected in forms of cardiomyopathy with a reversible trajectory such as fulminant myocarditis and other forms of nonischemic dilated cardiomyopathy. Hypotheses for the unexpected recovery after LVAD implantation in these reports include concurrent implementation of measures that could lead to reverse remodeling such as aggressive use of beta blockers and angiotensin-converting-enzyme inhibitors, cardiac resynchronization therapy, LV unloading prior to the necrotic and fibrotic stages of anthracycline-induced cardiomyopathy, and misdiagnosis of the etiology

of cardiomyopathy. Although these reports are of interest and suggest a partially reversible potential of anthracycline-induced cardiomyopathy, they do not give insight into the overall success rate and outcomes of MCS.

Recently, Oliveira et al. reported on the characteristics and outcomes of a cohort of patients with CCMP undergoing MCS [19]. The authors queried The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) to retrospectively identify patients with presumed CCMP cardiomyopathy who underwent MCS. Participation in this registry is mandatory in the United States for MCS implantation centers to gain approval from the Centers for Medicare and Medicaid Services. Between June 2006 and March 2011, the authors were able to identify 75 patients (2%) with CCMP out of 3812 with other causes of cardiomyopathy.

The baseline characteristics of CCMP patients undergoing MCS therapy paralleled those of CCMP patients undergoing OHT. The majority of CCMP patients (52%) had a history of breast cancer and 33% had a history of lymphoma or another hematological cancer. CCMP patients undergoing implantation of MCS devices were much more likely to be females (72% in the CCMP group versus 24% and 13%, resp., in the NICM and ICM groups) and had less comorbidity such as diabetes and tobacco use. Interestingly, the use of ICDs was significantly lower in the CCMP group than in the ICMP and NICM groups [19].

The longitudinal therapeutic goals of MCS support can be classified as follows: a bridge to cardiac transplantation, a bridge to cardiac recovery, lifelong therapy (also referred to as "destination" therapy), and a bridge to candidacy for cardiac transplantation. In the cohort studied by Oliveira et al., a greater proportion of patients with CCMP underwent MCS implantation as destination therapy than did patients with NICMP and ICMP [19]. Importantly, CCMP patients undergoing MCS implantation as destination therapy had significantly reduced survival compared to those receiving MCS as BTT (32% death rate versus 22% death rate in DT versus BTT patients, resp.) [19]. Prior studies have shown that a history of solid organ malignancy is associated with up to 89% greater likelihood of early death after DT LVAD implantation compared to those without a history of solid organ malignancy [20]. Why a history of malignancy in recipients of destination therapy MCS is associated with a greater risk of death requires further exploration. Specifically, elucidating whether poorer survival is related to competing cancer mortality, a higher burden of comorbidities, frailty, nutritional status, or greater risks of post-implantation complications such as bleeding, infection, and thrombosis will be important to guide patient selection for this costly therapy.

5. Need for Right Ventricular Assist Device (RVAD)

Oliveira et al. showed that a significantly greater proportion of CCMP patients required RVAD either concomitantly or following LVAD implantation. Specifically, 19% of CCMP versus 9.3% of non-CCMP patients ($p < 0.001$) required RVAD perioperatively [19]. The need for greater right ventricular failure in this patient population may be due to several causes.

First, it may reflect the pathophysiological process underlying anthracycline-induced cardiomyopathies, including proportionate deterioration of RV and LV functions in anthracycline-induced cardiomyopathy compared to the LV predominance observed in other causes of cardiomyopathy. The biventricular nature of anthracycline-mediated cardiomyopathy has been demonstrated in cardiac imaging studies [21–23]. Poorer right ventricular function around the time of MCS implant may also reflect predilection for clinicians to delay advanced therapies in patients with a history of recently treated cancer. Finally, poorer RV function may reflect higher incidences of pulmonary hypertension related to prior pulmonary emboli in patients with a history of cancer. This hypothesis was not supported by the Oliveira et al. study, which showed similar pulmonary vascular resistance in the CCMP group and the NICMP/ICMP groups prior to MCS implantation. Nevertheless, the important observation of greater need for RVAD in CCMP patients emphasizes the need for vigilance regarding the status of the right ventricle on the part of clinicians caring for patients with anthracycline-induced cardiomyopathy. This is particularly important because biventricular mechanical support is currently not feasible or approved as destination therapy and morbidity and mortality increase significantly with right ventricular failure after LVAD implantation.

Despite higher rates of post-MCS bleeding rates and a greater need for RVAD in the CCMP group, Oliveira et al. showed similar overall survival between all groups.

6. Surgical Considerations to MCS in Patients with Chemotherapy-Induced Cardiomyopathy

The feasibility of MCS may be affected by several technical considerations. Median sternotomy is required for the implantation of most contemporary continuous flow LVADs including Heart Mate II (Thoratec Corporation; Pleasanton, CA) and HeartWare (HeartWare International, Inc., Framingham, MA). Prior radiation therapy is an important consideration for sternotomy in CCMP patients being considered for MCS. A history of thoracic radiation therapy itself is a risk factor for developing cardiomyopathy after anthracycline therapy [24, 25]. High-dose thoracic field radiation therapy for breast cancer and lymphoma can lead to severe postradiation sternal damage. Under these circumstances, median sternotomy may be associated with a prohibitive risk of surgical complications including postoperative deep sternal wound infections [26]. Because there is a broad spectrum of mediastinal radiation-induced injury, ranging from minor fibrosis to heavy scarring and fusion of mediastinal structures including pericardial, myocardial, vascular and valvular damage, the extent of this injury should be taken into consideration in patients with a history of prior radiation therapy [27]. Although experience with minimally invasive, off-pump approaches to LVAD implantation is increasing, particularly with HeartWare devices [26], such approaches are not currently approved and are limited by the frequent need to address coexisting cardiac lesions including tricuspid

Table 1: Factors that may influence outcome after advanced heart failure therapies in adult patients with anthracycline-induced cardiomyopathy [1].

Patient characteristics that may favor advanced heart failure therapies in anthracycline-induced end-stage heart failure	Patient characteristics that may oppose advanced heart failure therapies in anthracycline-induced end-stage heart failure
Lower body surface area	Higher rates of malignancy*
Lower likelihood of diabetes	Higher rates of infection
Lower likelihood of hypertension	Impact of prior thoracic radiation therapy on sternotomy complications
Lower likelihood of smoking	Greater need for right ventricular assist device
	Higher rates of perioperative bleeding
Younger age	Higher rates of destination-therapy (as opposed to bridge to transplantation)#

*Applies to orthotopic heart transplantation but not left ventricular assist device.
#Applies to left ventricular assist device but not to orthotopic heart transplantation.

and aortic insufficiency and patent foramen ovale/atrial septal defect at the time of LVAD implantation.

7. Patient Size and Body Habitus

A potentially relevant observation in studies of LVAD and OHT in CCMP patients is the significantly lower body surface area (BSA) in patients with CCMP compared to those with other forms of cardiomyopathy. BSA was 12% lower in patients with CCMP undergoing LVAD implantation in the study by Oliveira et al. (BSA was 1.84 m^2 in the CCMP group versus 2.09 m^2 in the group with other forms of cardiomyopathy, $p < 0.0001$) [19]. Several factors may have contributed to this observation including the greater proportion of women and the effects of previous cancer treatment on growth in the case of pediatric acute lymphocytic leukemia. Indeed, growth deficit is a known complication of both anthracycline therapy and cranial irradiation in pediatric acute lymphocytic leukemia survivors [28]. Implantation of LVADs was previously restricted to patients with a body surface area >1.5 m^2. Fortunately, the continuous flow LVADs have demonstrated a good safety profile in patients as with BSA that is as low as 1.3 m^2 allowing for the use of nonpulsatile VADS in a significantly higher proportion of women, smaller adults, and adolescents [29]. Furthermore, the HeartWare device, which is implanted within the pericardium, has essentially eliminated small BSA restrictions to LVAD implantation [29]. Nevertheless, lower BSA has been shown to be associated with poorer outcomes and higher stroke risk after continuous flow LVAD implantation [30]. Finally, the observation of greater rates of right ventricular failure in this patient population makes Total Artificial Heart (TAH, SynCardia Systems Inc., Tucson, AZ) an important consideration. However, SynCardia Systems, Inc., recommends a minimum patient body surface area (BSA) of 1.7 m^2 [31]. Future studies are needed to determine if there is an important proportion of patients with a history of anthracycline-induced chemotherapy that are excluded from MCS due to small body surface area or, on the other hand, whether lower BSA reflects lower rates of obesity.

8. Conclusions and Future Directions

This case demonstrates the potential and unique challenges associated with the management of advanced heart failure in patients with a history of cancer and probable anthracycline-induced chemotherapy. The oncologic prognosis influenced the decision to defer LVAD and pursue home IV inotropes. However, when faced with another acute decompensation, LVAD was implanted but at a point when right ventricular dysfunction had progressed significantly. In retrospect, several clinical and hemodynamic parameters have been shown to predict right heart failure (such as elevated central venous pressure-to-pulmonary capillary wedge pressure ratio and right ventricular dysfunction on echocardiography) were present [32–35]. It remains unclear whether anthracycline-based chemotherapy in and of itself is a risk factor for right ventricular failure. It is possible that preemptive RVAD or TAH implantation could have mitigated her clinical demise. TAH was not an option as its use is approved only as a bridge to transplantation. TAH was also not an option due to her small body habitus. Finally, options related to end-of-life care such as nonhospice palliative care or hospice care could have been presented at an earlier point in the patient's clinical course. Therefore, this case exemplifies many of the complexities associated with advanced heart failure in patients with a history of cancer, particularly those who are not transplant candidates.

As a whole, patients with CCMP appear to have similar survival after OHT/LVAD therapy, respectively, compared to patients with other etiologies of cardiomyopathy. This is despite higher rates of malignancy after OHT and a greater need for RVAD after LVAD implantation. A history of cancer and end-stage heart failure should not preclude thoughtful and timely consideration of advanced therapies for end-stage heart failure. Rather, a comprehensive multidisciplinary approach that integrates the wishes and values of the patient with anticipation of potential complications should facilitate optimal care. Based on the current body of evidence, the various factors that may influence decision-making and outcomes after OHT and LVAD for anthracycline-induced end-stage heart failure are summarized in Table 1.

It is important to note that the overall evidence presented in this review is limited both by the very small number of studies and by retrospective nature of these studies. Furthermore, there is a paucity of data on outcomes of MCS in patients who are not eligible for transplant. In anticipation of a growing number of patients surviving long enough following cancer treatment to experience the cardiotoxic side effects of their cancer treatment, advanced therapies for end-stage heart failure in this patient population should be an intense focus of future research.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Exercise Prevention of Cardiovascular Disease in Breast Cancer Survivors

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Thanks to increasingly effective treatment, breast cancer mortality rates have significantly declined over the past few decades. Following the increase in life expectancy of women diagnosed with breast cancer, it has been recognized that these women are at an elevated risk for cardiovascular disease due in part to the cardiotoxic side effects of treatment. This paper reviews evidence for the role of exercise in prevention of cardiovascular toxicity associated with chemotherapy used in breast cancer, and in modifying cardiovascular risk factors in breast cancer survivors. There is growing evidence indicating that the primary mechanism for this protective effect appears to be improved antioxidant capacity in the heart and vasculature and subsequent reduction of treatment-related oxidative stress in these structures. Further clinical research is needed to determine whether exercise is a feasible and effective nonpharmacological treatment to reduce cardiovascular morbidity and mortality in breast cancer survivors, to identify the cancer therapies for which it is effective, and to determine the optimal exercise dose. Safe and noninvasive measures that are sensitive to changes in cardiovascular function are required to answer these questions in patient populations. Cardiac strain, endothelial function, and cardiac biomarkers are suggested outcome measures for clinical research in this field.

1. Introduction

Breast cancer is the most common malignancy among women worldwide [1], and an estimated 1% of the population are survivors of breast cancer [2]. Advances in breast cancer therapy have contributed to dramatic improvements in survival, but many of these therapies, particularly anthracycline chemotherapy, left-sided radiotherapy, and trastuzumab targeted therapy, are associated with cardiovascular toxicities [3]. Breast cancer survivors are at increased risk of cardiovascular disease-related death compared to women without breast cancer [4], likely due in part to these toxicities. An increased prevalence of traditional cardiovascular risk factors in this population at diagnosis, and lifestyle perturbations associated with cancer treatment also contribute to this increased risk [3]. Chemotherapy for breast cancer will induce menopause in one- to two-thirds of women [5], further increasing cardiovascular risk [1, 6]. As breast cancer survival rates rise, cardiovascular disease becomes an increasingly important competing risk [7]. Combined, these factors contribute to the recent finding that cardiovascular disease has surpassed breast cancer as the leading cause of death in older women diagnosed with breast cancer [8].

Current strategies to mitigate cardiotoxicity associated with anthracycline treatment include dose reduction, modified administration methods, liposomal formulations, and administration of cardioprotective medications [9]. However, dose modification may be associated with reduced oncological benefit [10], and pharmacological interventions may be associated with additional side effects.

Aerobic exercise training and other forms of physical activity are effective in primary and secondary prevention of cardiovascular disease and cardiovascular disease-related death [11]. For breast cancer survivors, exercise training is safe and effective in improving cardiorespiratory fitness, strength, body composition, fatigue, anxiety, depression,

and quality of life, and is recommended during and after treatment [12]. However, the effect of aerobic exercise on cardiovascular function and outcomes during or after breast cancer treatment is not well established in humans.

The purpose of this paper is to (1) review the potential mechanisms mediating exercise prevention of cardiovascular toxicity; (2) review the available evidence for the role of exercise in prevention of cardiovascular disease in breast cancer survivors, including predominantly preclinical studies of the heart and clinical studies of cardiovascular risk factors; and (3) suggest outcome measures for translation of the preclinical findings to clinical studies.

2. Potential Mechanisms Mediating Exercise Prevention of Cardiovascular Toxicity

The vast majority of studies investigating exercise prevention of direct cardiovascular toxicity are in rodent models utilizing the anthracycline agent doxorubicin and compare an exercise-trained treated group to a sedentary treated group. The discussion of mechanisms and preclinical evidence refers to studies with this design unless otherwise noted. The mechanism underlying the cardioprotective effects of aerobic exercise before or during treatment with doxorubicin has not been fully elucidated but is likely to be multifactorial with summative effects and feedback from diverse processes. Potential mechanisms by which exercise may act in opposition to the negative effects of doxorubicin to protect the heart and vasculature are listed in Table 1. There is available evidence for exercise protection mechanisms related to reduced oxidative stress, interruption of topoisomerase-mediated pathways, cardiomyocyte contractile protein isoform shifts, and upregulation of heat shock proteins (HSP), endothelial nitric oxide (NO), and endothelial progenitor cells.

The most widely supported mechanism by which exercise may prevent doxorubicin cardiotoxicity is through its antioxidant effects. The production of reactive oxygen species (ROS) is one of the possible mechanisms for doxorubicin cardiotoxicity [13, 14]. Although cells are equipped with an endogenous antioxidant system to protect against ROS, cardiomyocytes have only one fourth of the antioxidative capacity of the liver and other tissues [15], making them particularly vulnerable to oxidative stress. Exercise-induced enhancement of cardiomyocyte antioxidant capacity may prevent ROS-induced damage associated with doxorubicin treatment [16]. Compared with untrained animals, exercise-trained rodents have increased levels of antioxidant activity and reduced levels of oxidative stress markers following doxorubicin exposure [17–22]. However this mechanism may not play a role in cardioprotection when exercise is of low intensity and duration [23]. Reduced levels of protein turnover via the ubiquitin-proteasome pathway, an important mechanism for degradation of cellular proteins with oxidative damage, have been demonstrated in exercise-trained rodents compared to sedentary rodents [24]. This finding provides further support for exercise protection via reduced oxidative stress.

Anthracycline-induced ROS cause lipid peroxidation [25] and downregulate expression of the sarcoplasmic reticulum calcium pump, SERCA2a [14]. Decreased calcium uptake by SERCA2a then leads to an increase in cytosolic calcium [14]. These two changes result in opening of the mitochondrial permeability transition pore, allowing release of calcium from the mitochondrial matrix, downregulation of mitochondrial respiration, and leaking of proapoptotic mitochondrial proteins into the cytosol [26, 27]. A single submaximal exercise session 24 hours before doxorubicin treatment prevented opening of the mitochondria permeability transition pore, mitigating the downstream effects [26]. This hypothesis is supported indirectly by several other studies demonstrating attenuation of doxorubicin-associated increases in the proapoptotic proteins caspase-9 and 3 in exercise trained rodents [18, 23, 24, 26]. These findings may be related to modulation of defense systems including stress chaperones like HSPs, or antioxidants, but may not be related to exercise-induced upregulation of SERCA2a [28, 29].

There is emerging evidence implicating topoisomerase 2β, an enzyme regulating DNA unwinding, in doxorubicin-induced cardiomyocyte mitochondrial dysfunction [30], secondary to downregulation of peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, a transcriptional coactivator of mitochondrial biogenesis [31]. Exercise training upregulates expression of PGC-1α in skeletal muscle, although a similar response in cardiomyocytes has not been observed [32, 33]. Two recent preclinical studies investigating the role of PGC-1α in exercise cardioprotection did not demonstrate an interaction between exercise and doxorubicin [22, 34]. However, the capacity of exercise to impact topoisomerase 2β and PGC-1α in cardiomyocytes requires further investigation before this mechanism can be dismissed.

In the rodent heart, doxorubicin causes disruption of cardiac bioenergetics and an associated shift from the α isoform of the contractile protein, myosin heavy chain (MHC), to the β isoform which has reduced contractile power [35]. Exercise training before [28, 35] and during doxorubicin treatment [36, 37] conserves the α isoform in rats. However, healthy human hearts express 7% of the α isoform on average, while this is the predominant isoform expressed in the rat heart [38]. Therefore the extent and subsequent impact of a doxorubicin-induced shift in MHC isoform distribution may be smaller for human myocardium. Clinical research is required to clarify the role of prevention of MHC isoform shifts in exercise cardioprotection.

HSPs control protein folding and unfolding, and are upregulated in cardiomyocytes during times of oxidative stress [24]. An exercise-induced increase in HSP expression is hypothesized to play a role in cardioprotection against doxorubicin by preserving the integrity and activity of mitochondrial respiratory complexes and thereby attenuating mitochondrial dysfunction [39]. Although there is some evidence supporting HSP-mediated cardioprotection [17, 19, 23], there are also conflicting results [19, 24, 40].

Breast cancer therapies, including chemotherapy, targeted therapies, and radiotherapy, may be associated with endothelial dysfunction, a disease process involving impaired

Table 1: Potential mechanisms for exercise prevention of doxorubicin-related cardiovascular toxicity.

Myocardial target	Role of target	Direction of exercise-induced change*	Direction of doxorubicin-induced change*	Evidence of exercise prevention of doxorubicin-induced change
Mechanisms with evidence for their role in exercise prevention				
Antioxidant to oxidative stress ratio	Prevention of oxidative damage	↑ [15]	↓ [13]	✓ [17–21, 52] × [23]
Expression of $\alpha : \beta$ myosin heavy chain isoform in rodents	Motor protein required for muscular contraction; in a healthy rodent heart there is a much higher concentration of the α isoform	↑ [154]	↓ [155]	✓ [28, 35–37] × [23]
Caspase 3 and 9 activity	Markers for apoptotic signaling	↓ [156]	↑ [14]	✓ [18, 23, 24, 26]
HSP 60 expression	Controls protein folding and unfolding in response to stress	↑ [18]	↑↑ [19]	✓ [17, 19]
Mitochondrial permeability transition pore opening	Regulation of calcium handling and apoptosis	↓ [157]	↑ [158]	✓ [26]
Ubiquitin-proteasome activation	Maintains protein function and quality control	↓ [159]	↑ [160]	✓ [24]
Endothelial progenitor cell level	Physiologic and pathologic vessel formation	↑ [54]	↓ [161]	✓ [55]
HSP72 expression	Controls protein folding and unfolding in response to stress	↑ [18, 162]	= [163]	✓ [23] × [24, 40]
SERCA2a expression	Calcium recycling from the cytosol into the sarcoplasmic reticulum	↑ [164]	↓ [165]	✓ [166] × [28, 29]
Mechanisms with evidence against their role in exercise prevention				
HSP 70 expression	Controls protein folding and unfolding in response to stress	↑ [167]	↓ [168]	× [19]
AMPK activation	Senses and regulates energy homeostasis	↑ [169]	↓ [170]	× [166]
Cardiac progenitor cell level/heart mass	Physiological turnover of cardiomyocytes	↑ [171]	↓ [172]	× [29]
Expression of PGC-1α	Transcription coactivator that regulates mitochondrial biogenesis and angiogenesis	= [32, 33]	↓ [173]	× [22, 34]
Potential mechanisms for exercise prevention lacking investigation				
Neuregulin-1/ErbB4 signalling	Cardiac cell survival growth factor	↑ [60]	↓ [174]	∅
Expression of GATA-4	Transcription factor involved in cardiac survival, hypertrophic growth of the heart	↑ [58]	↓ [175]	∅

↑: increase; ↓: decrease; =: no change; ✓: evidence available in favor of this mechanism; ×: evidence available against this mechanism; ∅: no evidence available. HSP: heat shock protein; SERCA: sarcoplasmic reticulum calcium pump; AMPK: AMP-activated protein kinase; PGC: peroxisome proliferator-activated receptor-γ coactivator.

*Note: Where possible reference cited provides evidence for the cardiomyocyte response, which may differ from other cell types.

regulation of vascular tone and loss of atheroprotection [41]. Flow-mediated dilatation is triggered by shear stress from increased blood flow through a vessel, resulting in NO-mediated vasodilation [42]. Doxorubicin impairs both endothelium-dependent (i.e., flow-mediated) and endothelium-independent vasodilation [41, 43, 44]. Breast radiation impairs endothelium-dependent vasodilation in exposed axillary arteries, causes ultrastructural damage to myocardial capillaries, and can induce atherosclerosis in coronary arteries [45–48]. Trastuzumab may cause endothelial dysfunction through reductions in NO [49].

Exercise training improves endothelial dysfunction, predominantly through increased NO production as a result of chronic periods of pulsatile blood flow [50]. In the presence of the superoxide ROS, NO reacts to form a reactive molecule that can damage DNA, and this reaction also decreases the bioavailability of NO [51]. The upregulation of antioxidative enzymes associated with exercise training may therefore promote NO bioavailability by scavenging ROS [51]. Hayward et al. provided evidence that exercise preconditioning prior to 5-fluorouracil chemotherapy exposure increased NO production in rodents [52].

Endothelial progenitor cells (EPCs) contribute to maintaining the integrity of the endothelial cell layer, and lower levels of circulating EPCs are associated with an increased risk of cardiovascular events and death [53]. Exercise stimulates EPC mobilization from the bone marrow [54]. In human breast cancer survivors receiving doxorubicin-containing chemotherapy, exercise has been associated with an increase in circulating EPCs relative to usual care controls [55].

There are other proposed mechanisms for cardiotoxicity where exercise training could counteract the doxorubicin-induced molecular response that have not yet been investigated as mechanisms for exercise cardioprotection. For example, pharmacological α1-adrenoceptor activation of the cardiac transcription factor GATA-4 has demonstrated cardioprotective capacity against doxorubicin [56]. Therefore, exercise training, which appears to enhance both α1-adrenoceptor responsiveness [57], and GATA-4 mRNA level in the heart [58] may also exert a cardioprotective effect via a GATA-4 pathway. Another example includes doxorubicin and trastuzumab downregulation of neuregulin-1/ErbB4 receptor tyrosine kinase signaling in cardiomyocytes. Neuregulin-1/ErbB4 signaling plays a critical role in cardiac development and cardiomyocyte survival and organization [59]. Intriguingly, exercise training upregulates expression of neuregulin-1 in rodent cardiomyocytes [60], indicating a potential mechanism for exercise prevention of doxorubicin- and trastuzumab-related cardiotoxicity. Readers are referred to a more comprehensive review of potential mechanisms for exercise prevention of targeted cancer therapy-related cardiotoxicity [61].

In summary, although evidence exists for several different mechanisms through which exercise protects the heart and vasculature from doxorubicin-related toxicity, the unifying feature appears to be increased antioxidant capacity and reduction of oxidative stress. Several potential mechanisms, including exercise-induced upregulation of topoisomerase 2β/PGC-1α, GATA-4, and neuregulin-1/ErbB4 warrant further investigation to determine their role in cardioprotection.

3. Evidence for Exercise Prevention of Cardiovascular Disease

3.1. Cardiotoxicity Prevention

3.1.1. Acute Exercise. In animal models, doxorubicin-related cardiotoxicity can be attenuated by a single exercise session in close proximity to time of exposure. In the seminal study in this area, a 30-minute exercise session completed half an hour after doxorubicin exposure reduced mortality [62]. These findings were extended to demonstrate that an exhaustive exercise session half an hour after doxorubicin exposure attenuated markers of cardiomyocyte mitochondrial dysfunction [63]. Sixty minutes of submaximal exercise performed 24 hours prior to doxorubicin prevented or attenuated left ventricular (LV) systolic and diastolic dysfunction, cardiomyocyte mitochondrial apoptosis and dysfunction, and lipid peroxidation at 5 days post-treatment in rodents [26, 64].

The potential of a single exercise session to provide cardioprotection is particularly appealing, as regular, supervised exercise training during chemotherapy may not be feasible for all patients due to distance from home to exercise centers, difficulty with treatment symptoms, scheduling conflict with work, or family obligations. Ongoing research by our group is investigating the cardioprotective benefit of an acute exercise session 24 hours prior to doxorubicin administration in women with breast cancer.

3.1.2. Exercise Training before Treatment. In animals receiving high-dose bolus doxorubicin, exercise preconditioning prevents or attenuates acute (~24 hour post) increases in cardiac troponin I [17, 18], markers of oxidative stress [17–21, 24, 65], cardiomyocyte mitochondrial dysfunction [18, 19, 24], morphological and histological damage [16], markers of apoptosis [18, 24, 66], and decreases in HSP expression [17, 19] and LV systolic function [40, 65]. Similar findings have been reported in studies that extended the follow-up time to 5–10 days after doxorubicin exposure [35, 40, 67, 68]. Findings exclusive to studies with longer follow-up include attenuation of deficits in coronary flow [40], transmitral, and transaortic flow [35, 67], as well as transformation to the β-MHC isoform [35]. Even at four weeks after doxorubicin exposure, the beneficial effects of exercise preconditioning on β-MHC transformation, LV wall thickness, mass and systolic function, and transmitral/transaortic flow were still apparent [28].

The feasibility of exercise preconditioning in humans has been questioned, as the interval between breast cancer diagnosis and treatment is shorter than the length of most training programs that have been studied (8 to 14 weeks). However, cardioprotective effects have been reported after as little as 5 days to 3 weeks of training in rodents [21, 24, 66]. It should be noted that administered doxorubicin doses in these studies were higher than comparable human doses. It

is unclear whether similar benefits would be seen in patients receiving standard treatment doses.

3.1.3. Exercise Training during Treatment. Exercise training concurrent to chronic doxorubicin treatment in rodents has been associated with attenuation of LV systolic and diastolic dysfunction [23, 29, 37, 69, 70], cardiomyocyte apoptosis [23], transformation to β-MHC [36, 37], reductions in LV wall thickness [69] and heart mass [22], and deficits in coronary [23], transmitral, and transaortic flow [29, 37, 69].

Exercise training in humans during chemotherapy treatment for breast cancer is feasible and prevents the decrease in cardiorespiratory fitness seen in usual care controls [70–72]. Preliminary clinical studies of the effects of exercise training on cardiac function in humans undergoing breast cancer treatment have had disappointing results, however. A small randomized control trial of exercise training compared to usual care during doxorubicin-containing chemotherapy for breast cancer found no change in LV ejection fraction (LVEF) in either group [70]. A single-arm study investigated the effects of four months of exercise training in 17 breast cancer survivors receiving adjuvant trastuzumab therapy. Despite exercise training, trastuzumab was associated with LV dilatation and reduced LVEF [73]. However the exercise training dose may have been insufficient, as participants did not attend 41% of exercise sessions. More sensitive measures of cardiac function and a higher exercise dose are likely required in order to demonstrate a cardioprotective benefit in clinical studies.

3.1.4. Exercise Training after Treatment. Although Héon et al. have reported reduced markers of cardiomyocyte apoptosis and oxidative stress in rodents undergoing exercise training two weeks after the completion of doxorubicin administration [74], to our knowledge the effects of post-treatment exercise on cardiac function have not been studied.

3.1.5. Summary of Cardiotoxicity Prevention Evidence. In summary, acute and chronic exercise before, during or after doxorubicin treatment in rodents consistently results in prevention or attenuation of doxorubicin-induced deleterious effects to cardiomyocyte morphology and biochemistry, as well as cardiac function. Preclinical experimental research is needed to determine whether exercise can provide cardioprotection from cancer therapies other than doxorubicin.

3.2. Vascular Toxicity Prevention. Few studies have investigated the effects of exercise on vascular function during breast cancer treatment. Six weeks of exercise training, initiated four weeks after doxorubicin treatment, was associated with improved endothelium-independent but not endothelium-dependent vasodilation, and with reduced mortality in rats with cardiac dysfunction [75]. Similarly, eight, but not four weeks of exercise training prior to exposure to 5-fluorouracil chemotherapy was associated with enhanced endothelium-dependent vasodilation in rats [52]. In humans, two small randomized trials of the effect of exercise training during doxorubicin-containing chemotherapy on endothelial function have had conflicting results [55, 70]. To advance understanding of exercise prevention of cardiovascular disease in breast cancer survivors, future exercise cardioprotection studies should include measurement of vascular function in addition to the cardiac measures.

3.3. Cardiovascular Risk Factors Modification. Traditional cardiovascular risk factors should be monitored and managed in breast cancer patients who receive cardiotoxic cancer therapies to prevent additional injury [76]. Exercise can favorably improve a number of cardiovascular risk factors including hypertension, raised cholesterol/lipids, overweight and obesity, raised blood glucose or diabetes, and cardiorespiratory fitness [77].

Hypertension is more than twice as prevalent among breast cancer survivors aged 55 and older as it is among the general population [78], and may be caused by chemotherapy agents used to treat breast cancer including cyclophosphamide, cisplatin and carboplatin [79]. Chemotherapy for breast cancer is also associated with elevations in triglyceride levels [80], while tamoxifen treatment may reduce levels of protective high density lipoprotein (HDL) [81]. Prior to treatment, breast cancer survivors may already have a suboptimal lipid profile including higher total cholesterol, triglyceride, and low density lipoprotein levels, and lower HDL levels than healthy controls [82–86]. A similar pattern occurs with overweight or obesity, where overweight, a risk factor for development of breast cancer [87], is often an issue prior to treatment, and chemotherapy treatment perpetuates the problem via its association with greater weight gains than other treatments in the year following diagnosis [88]. Therefore, it is not surprising that almost half of breast cancer survivors are overweight or obese [89]. Treatment also has lasting adverse effects on peak oxygen consumption (VO_2), the gold standard measurement of cardiorespiratory fitness [90]. Chemotherapy causes a 6–10% reduction in peak VO_2 [71, 91], and following breast cancer treatment completion, remains an average of 22% lower than that of healthy sedentary controls [92]. Furthermore, the level of cardiorespiratory fitness amongst breast cancer survivors appears to mediate incidence of cardiovascular disease and risk factors [93]. Lastly, breast cancer survivors are at an increased risk for diabetes from two up to 10 years following diagnosis [94], and its presence increases the risk of mortality in this population [95]. In early stage breast cancer survivors, high blood insulin levels, indicative of insulin resistance, are associated with obesity, poor lipid profiles [96], distant recurrence and death [97].

A number of exercise intervention studies in human breast cancer survivors have included cardiovascular risk factors as outcome measures. Exercise interventions in breast cancer survivors have consistently reported decreases in systolic blood pressure of 3–5 mmHg both during [98–100] and after [99, 101–105] treatment. Reported effects on blood lipids following an exercise intervention with or without dietary intervention include significant positive effects on triglycerides [102, 105], and HDL [105], or no effect [104, 106,

107]. Numerous exercise interventions have measured weight or body composition change with mixed results, showing either no effect or weight reduction [12]. Small feasibility studies have demonstrated that the combination of exercise with a diet intervention could be more effective in reducing weight in breast cancer survivors [106, 107]. Exercise training during chemotherapy or radiation treatment for breast cancer at minimum can prevent the peak VO_2 decline occurring in usual care controls [71], or improve peak VO_2 [70, 72, 91, 108, 109]. Exercise training following completion of breast cancer treatment improves peak VO_2 [106, 110, 111]. Only one [105] of six randomized controlled trials to examine the effect of an exercise intervention on insulin and/or insulin resistance demonstrated statistically significant changes [104, 107, 112–114]. This same study also reported improvements in fasting blood glucose [105].

In summary, exercise interventions appear to have clinically meaningful effects on blood pressure and peak VO_2, whereas the effects on blood lipids, weight, and insulin/glucose and potential development of diabetes are less clear. The strong established relationships between both blood pressure and peak VO_2 and cardiovascular disease development and mortality in noncancer populations [6, 115–117] provide convincing support for the role of exercise in prevention of cardiovascular disease in human breast cancer survivors.

4. Translation of Preclinical Findings to Clinical Studies

Substantial preclinical evidence supports the role of exercise in prevention of cardiovascular disease toxicity, and there is some evidence for modification of cardiovascular risk factors in clinical trials. Further clinical research is warranted to determine whether exercise is a feasible and effective method for the reduction of cardiovascular morbidity and mortality in breast cancer survivors. Barriers to the translation of preclinical findings to human models include the need for more sensitive outcome measures and uncertainty regarding the optimal exercise dose.

Demonstration of the cardioprotective benefits of exercise in rodents has typically required euthanasia. One of the greatest barriers to this research in humans is identification of a noninvasive and sensitive outcome measure. Three-dimensional echocardiography-derived LVEF has emerged as a more reliable measure of LV function in patients receiving chemotherapy compared to traditional two-dimensional imaging [118], although this does not necessarily imply greater sensitivity to early changes in function. Echocardiography-derived LV global longitudinal strain and strain rate are able to detect changes in cardiac function during chemotherapy, radiation and trastuzumab treatment before changes in LVEF are detectable [119]. In noncancer populations, cardiac strain responds to exercise training [120]. Our research group is conducting an ongoing study to determine whether exercise training can prevent the doxorubicin-related decline in cardiac strain parameters in women with breast cancer. These parameters are widely available in conjunction with standard echocardiography [121]; with acceptable inter- and intra-observer variability (5% and 3.5%, resp.) [122]. Global longitudinal strain is predictive of all-cause mortality for a number of other cardiac conditions [123–126], and may be a stronger predictor of outcomes than LVEF [123, 126], but its relationship with clinical outcomes other than LVEF in breast cancer survivors is unknown.

Endothelial function is another attractive clinical outcome measure because dysfunction is an early process in the development of cardiovascular disease, and in noncancer populations, responds to pharmacological [42, 127] and exercise [50] interventions. Endothelial function can be easily measured in humans with a reactive hyperemia test, in which a cuff is inflated around the arm to occlude blood flow for 5 minutes. With release, the sudden increase in blood flow causes vasodilatation, which can be measured with ultrasound or peripheral arterial tonometry [127].

Cardiac biomarkers may play a role in predicting and identifying cardiotoxicity [128]. N-terminal prohormone brain natriuretic peptide (NT-proBNP) is frequently elevated during and after anthracycline treatment in adults [129–131]. There is mixed evidence regarding its ability to predict cardiac dysfunction following anthracycline treatment [130–132], as several studies where trastuzumab treatment followed anthracycline treatment, do not report a predictive ability of NT-proBNP [122, 133–135]. Due to inter-individual variations in kinetics, several measurements may be required to capture an elevation in cardiac troponins in patients receiving anthracyclines [122, 129, 130, 133, 134, 136–146], but the occurrence of an elevation in troponin I is predictive of chemotherapy and trastuzumab-related decreases in LVEF [139, 147], and cardiac events [140]. Exercise in heart failure patients does not change levels of NT-proBNP [148] or cardiac troponin I [149], but chronic heart failure has a different pathophysiology than the acute effects of cardiotoxic cancer therapies. Nonetheless, cardiac biomarkers may prove to be an effective outcome measure for exercise cardioprotection interventions due to their accessibility and reliability as a marker of cardiotoxicity.

Another important factor in the effective translation of preclinical findings to humans is the exercise intervention design. While preclinical and clinical experimental studies demonstrate that high intensity aerobic exercise results in greater cardiac benefits than moderate or low intensity [150, 151], the strenuous exercise prescription applied in most preclinical studies (five days a week, moderate to high intensity, 20–90 minutes) would likely not be tolerable for humans undergoing chemotherapy treatment [152]. One rodent study implemented a more clinically feasible and practical exercise prescription and doxorubicin treatment protocol involving 20 minutes of low intensity exercise, performed five days per week during chronic low dose doxorubicin treatment [23]. Although the lower doxorubicin dose failed to induce the MHC isoform shift and lipid peroxidation reported with higher doses, the lower exercise dose was protective against LV dysfunction and cardiomyocyte apoptosis [23]. In heart failure patients, moderate intensity exercise performed three days per week has been shown to improve systolic function [153]. Therefore, the required exercise dose for

cardioprotection likely involves three to five days per week of moderate to high intensity aerobic exercise of at least 20 minutes in duration, but greater benefits will likely occur with higher doses. The optimal prescription requires a balance of patient tolerance with protective efficacy.

5. Conclusion

Breast cancer therapy has efficacious antitumor effects, but is associated with increased risk of cardiovascular disease. A considerable body of research, including preclinical studies and clinical trials, indicates that exercise may be an effective nonpharmacological method of attenuating the harmful effects of breast cancer therapies on the heart and vasculature, of modifying cardiovascular risk factors, and potentially reducing cardiovascular morbidity and mortality in this vulnerable population. The mechanisms for exercise prevention appear to be predominantly related to an increase in antioxidant capacity and associated reduction in oxidative stress. Clinical trials are needed to investigate the role of exercise in the prevention of direct cardiovascular toxicity of breast cancer treatment and the effect on cardiovascular events and mortality. The role of exercise in the prevention of cardiovascular disease in other cancer populations also warrants further research, as the detrimental combination of a high incidence of baseline risk factors combined with cancer treatment cardiovascular toxicity may be common to multiple cancer types. Echocardiographic quantification of LV global longitudinal strain and strain rate, endothelial function quantification, and measurement of circulating cardiac biomarkers are safe, noninvasive measures that may be sensitive and effective outcome measures for clinical studies of exercise prevention of breast cancer treatment-related cardiovascular toxicity. The exercise frequency, intensity, and duration demonstrating cardioprotection in most preclinical studies may need to be modified to accommodate human patient tolerability during ongoing cancer treatment.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

The Prevalence of Cardiac Risk Factors in Men with Localized Prostate Cancer Undergoing Androgen Deprivation Therapy in British Columbia, Canada

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Background. While androgen deprivation therapy (ADT) reduces the risk of prostate cancer-specific mortality in high-risk localized prostate cancer, it adversely affects cardiovascular (CV) risk factor profiles in treated men. *Methods.* We retrospectively reviewed the charts of 100 consecutive men with intermediate- or high-risk localized prostate cancer referred to the British Columbia Cancer Agency for ADT. Data on CV risk factors and disease were collected and Framingham risk scores were calculated. *Results*. The median age of the study cohort was 73 years. Established cardiovascular disease was present in 25% of patients. Among patients without established CV disease, calculated Framingham risk was high in 65%, intermediate in 33%, and low in 1%. Baseline hypertension was present in 58% of patients, dyslipidemia in 51%, and diabetes or impaired glucose tolerance in 24%. Hypertension was more prevalent in the study cohort than in an age- and sex-matched population sample (OR 1.74, $P = 0.006$); diabetes had a similar prevalence (OR 0.93, $P = 0.8$). *Conclusions.* Patients receiving ADT have a high prevalence of cardiovascular disease and risk factors and are more likely to be hypertensive than population controls. Low rates of CV risk screening suggest opportunities for improved primary and secondary prevention of CV disease in this population.

1. Introduction

Prostate cancer is the most common cancer diagnosed in men, affecting 1 in 7 men in North America [1, 2]. Androgen deprivation therapy (ADT) with gonadotropin releasing hormone (GnRH) agonists has been a mainstay of therapy for locally advanced and metastatic prostate cancer since the 1990s and is also increasingly used in the neoadjuvant setting prior to radiotherapy for early disease [3].

While ADT decreases the risk of prostate cancer-specific mortality in advanced prostate cancer, it is associated with a number of adverse metabolic effects. The risk of developing diabetes while on ADT increases by up to 44% [4, 5] as lean body mass is significantly reduced and replaced by increased fat mass [6, 7]. Several large population-based studies have indicated that men receiving ADT are at increased risk of fatal and nonfatal cardiovascular events [5, 8, 9]. Moreover, men with cardiovascular risk factors or previous cardiovascular events are at particularly high risk [9, 10].

No specific guidelines exist for the screening of patients with prostate cancer who have preexisting cardiovascular disease or who may be at risk for cardiovascular morbidity and mortality as a result of ADT. Studies have shown that cancer patients and survivors may be less likely to receive therapies directed at cardiovascular risk factor modification compared to other patients [11]. Underrecognition of risk factors and subsequent undertreatment may represent an important care gap in survivor populations. As such, appropriate treatment and modification of cardiovascular risk factors may minimize treatment related adverse effects. With this in mind, we investigated the burden of cardiovascular risk among patients receiving ADT for intermediate- and high-risk localized prostate cancer at our centre and described the measures taken to risk-stratify these patients prior to therapy.

2. Methods

2.1. Patient Population and Treatment. The study population included 100 consecutive men with intermediate- or high-risk prostate cancer who were referred to the British Columbia Cancer Agency (BCCA) between October 1, 2011, and October 31, 2012, and who were treated with combined ADT and radiotherapy with curative intent. Patients were included if they had been referred to an oncologist within 3 months of cancer diagnosis and if their treatment plan included curative intent radiotherapy and ≥6 months of ADT. Patients were excluded if they had metastatic prostate cancer. Radiotherapy protocols and choices of ADT regimens were at the discretion of treating physicians.

2.2. Data Collection. Data was collected by retrospective chart review. Data on patient demographics, past medical history, prior cardiac history, and medications were collected from the oncology chart. If a specific CV risk factor was not mentioned in the past medical history, the patient was presumed not to have that risk factor unless (1) the patient was on antihypertensive medications, in which case they were considered to have hypertension, or (2) the patient was on a statin medication or their lipid profile revealed an LDL ≥3.5 mmol/L or a non-HDL-C of ≥4.3 mmol/L, in which case they were considered to have dyslipidemia. Systolic blood pressure was recorded from the initial consult with the oncologist or from the anaesthesia before operative consult or other specialist consults if not available on the first visit. The electronic chart and the common provincial laboratory system were accessed to find any lipid profiles from the year prior to or concomitant with the start of ADT. Lastly, the presence of any CV investigations on the chart, either in the year prior to the initiation of ADT or in response to the start of ADT, as well as any referral to a cardiology or internal medicine service for cardiac assessment was recorded. The University of British Columbia Research Ethics Board approved the data collection protocol used in this study.

2.3. Risk Calculation. A Framingham risk score (FRS) [12] was calculated on all patients who did not have underlying coronary heart, cerebrovascular, or peripheral arterial disease (PAD) to estimate the 10-year risk of CV events. A modified Charlson Comorbidity Index [13] was calculated on all patients to estimate 10-year mortality risk. Prostate cancer diagnosis was not accorded any points in the modified Charlson score. If no blood pressure was recorded on the chart, a score of 0 was used for hypertension in the Framingham risk calculation. Because ADT is known to increase serum lipids, any lipid measurements taken after the start of ADT were not used in the Framingham risk calculation. If no lipid profile was available, a score of 0 was used for the HDL and total cholesterol values in calculating the FRS.

2.4. Comparison Cohort. The prevalence of two cardiovascular risk factors, hypertension and diabetes, was compared to values reported for males aged 65 years and over in British Columbia in the 2011-2012 Canadian Community Health Survey, administered by Statistics Canada [14]. These population prevalence values refer to the proportion of the population who reported that they had been diagnosed by a health professional as "having high blood pressure" or "having type 1 or type 2 diabetes," respectively.

2.5. Statistical Analysis. Proportions of men in the prostate cancer cohort and comparison cohort with hypertension and diabetes were compared using Chi-square tests. P values <0.05 were considered significant. Statistical analysis was performed using Microsoft Excel for Mac Version 14.4.6 (Microsoft Corporation, Redmond, WA).

3. Results

Baseline demographics for the study cohort are displayed in Table 1. The median age of the cohort was 73 years (range 50–87 years). Thirty (30%) subjects had moderately differentiated cancer (Gleason score 5–7) and 70 (70%) had poorly differentiated disease (Gleason score 8–10). The median initial PSA value was 12 ng/mL (IQR 8.2, 21.1). No patient had any evidence of metastatic prostate cancer on either bone scan or staging CT scan. Most patients (82%) had a modified Charlson Comorbidity Index of 0.

3.1. Baseline Cardiovascular Risk. Previously documented coronary artery disease (CAD) was present in 17% of patients, with 9 of these patients having had a past percutaneous coronary intervention (PCI) and 5 patients having undergone coronary artery bypass grafting (CABG) surgery. A history of stroke was present in 7%, and 5% had a history of PAD. A total of 25 patients were excluded from the Framingham risk calculation due to previous history of CAD, PAD, or stroke. A history of cardiac arrhythmia was documented in 10% of patients, 5 of whom had atrial fibrillation. The presence of baseline cardiac risk factors was common in this cohort (Table 2), with 58% of patients having a history of hypertension, 51% having a history of dyslipidemia, and 17% of patients having a history of diabetes. Only 4% of patients had no cardiac risk factors at all. Complete data to calculate a Framingham risk score was present for only 17% of patients; 62% of those studied did not have a lipid profile in the year prior to starting ADT and 58% did not have a blood pressure recording on the chart. Despite amending the Framingham risk calculation with scores of 0 for the missing data, only 1 patient was in the low risk Framingham category. Most patients, 69%, were in the high Framingham risk category and 30% were calculated to be at moderate Framingham risk.

3.2. Cardiovascular Investigations. Only 35% of patients had an ECG present on the chart (Figure 1). 22 of 35 ECGs were classified as normal. The most common abnormalities noted on ECG were nonspecific ST segment changes ($n = 5$), followed by intraventricular conduction delays or bundle branch block ($n = 3$). Less common was evidence of a prior myocardial infarct ($n = 2$) or left ventricular hypertrophy ($n = 2$). Only 6% of the patients studied had further testing for cardiac ischemia with either exercise treadmill testing or

Table 1: Baseline characteristics of 100 men referred for androgen deprivation therapy.

Age at diagnosis	73 (50–87)
Vascular disease	25 (25%)
Coronary artery disease	17 (17%)
Percutaneous coronary intervention	9 (9%)
Coronary artery bypass surgery	5 (5%)
Stroke	7 (7%)
Peripheral arterial disease	5 (5%)
Atrial fibrillation	5 (5%)
Supraventricular tachycardia	1 (1%)
Arrhythmia, not specified	4 (4%)
Cardiac pacemaker	1 (1%)
Pericarditis	1 (1%)
Coronary vasospasm	1 (1%)
History of heart failure	1 (1%)
Framingham risk category	
High risk	49 (65%)*
Intermediate risk	25 (33%)*
Low risk	1 (1%)*
Gleason score	
Moderately differentiated (5–7)	30 (30%)
Poorly differentiated (8–10)	70 (70%)
Clinical stage	
T1	27 (27%)
T2	43 (43%)
T3	23 (23%)
T4	3 (3%)
X	4 (4%)
Initial PSA (ng/mL)	
<5	9 (9%)
5–10	29 (29%)
>10	62 (62%)
Updated Charlson Comorbidity Index	
0	82 (82%)
1	14 (14%)
≥2	4 (4%)
Hormonal treatment used	
Goserelin	72 (72%)
Leuprolide	25 (25%)
Degarelix	2 (2%)
Bicalutamide	92 (92%)
Buserelin	1 (1%)
Flutamide	1 (1%)

Expressed as median (range) or number (percentage).
*Expressed as percentage of patients without baseline history of vascular disease.

myocardial perfusion imaging (Table 3). Documentation of a previous cardiology assessment was present for 6 patients, while 3 more patients were referred to a cardiology or internal medicine service for further work-up after oncology consult.

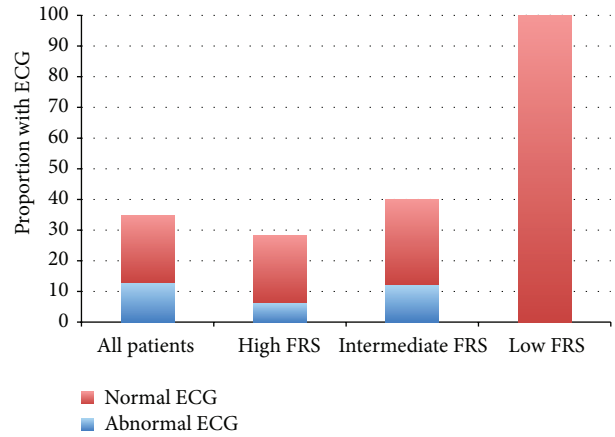

Figure 1: Proportions of patients referred for androgen deprivation therapy with normal and abnormal electrocardiograms available for review. ECG, electrocardiogram; FRS, Framingham risk score.

3.3. Comparison with Population Prevalence Values. In the 2011-2012 Canadian Community Health Survey, 44.3% (n = 139, 502) of men aged 65 years and over in British Columbia reported that they had been diagnosed with high blood pressure, and 18.0% (n = 56, 540) reported that they had been diagnosed with diabetes. Compared to the population sample, the odds ratio for having hypertension in our prostate cancer cohort was 1.74 (P = 0.006) and the odds ratio for having diabetes was 0.93 (P = 0.8).

4. Discussion

In this cross-sectional study of cardiovascular risk profiles among men referred for management of localized prostate cancer with ADT, we identified high prevalences of baseline cardiovascular risk factors and of cardiovascular disease. In addition to the 25% of men with established cardiovascular disease in our study population, at least 69% of subjects without established disease had a high FRS which is associated with a ≥20% 10-year risk of developing coronary heart disease, prior to initiation of ADT. By contrast, our cohort had a low prevalence of other comorbidities and a low expected mortality predicted by the Charlson Comorbidity Index.

We identified a higher prevalence of hypertension among our cohort than was reported among men aged 65 years and over in the same geographic area during the 2011-2012 Canadian Community Health Survey, suggesting that our prostate cancer population may be at higher risk of cardiovascular disease than members of the general population without prostate cancer, even after controlling for age and sex. The reasons for this association are not clear, but we can hypothesize that men with prostate cancer may have an increased burden of cardiovascular risk factors because many of these risk factors are also associated with risk of cancer. Indeed, previous studies have demonstrated increased prostate cancer risk among men with risk factors such as hypertension [15, 16], dyslipidemia [17], and the metabolic syndrome [15, 17, 18]. Increased prostate cancer risk has also

Table 2: Cardiac risk factors present in 100 men prior to receiving androgen deprivation therapy.

Risk factor	All patients ($n = 100$)	High FRS ($n = 49$)	Intermediate FRS ($n = 25$)	Low FRS ($n = 1$)
Hypertension	58 (58%)	28 (57%)	7 (28%)	0
Diabetes mellitus or IGT	22 (22%)	11 (22%)	6 (24%)	0
Cigarette smoking				
Never	46 (46%)	22 (45%)	14 (56%)	1 (1%)
Current	6 (6%)	3 (6%)	2 (8%)	0
Quit < 5 years ago	3 (3%)	1 (2%)	1 (4%)	0
Quit > 5 years ago	44 (44%)	23 (47%)	7 (28%)	0
Family history of CAD	10 (10%)	2 (4%)	0	0
Dyslipidemia	51 (51%)	19 (39%)	10 (40%)	0
Chronic kidney disease (GFR < 60 mL/min/1.73 m^2)	10 (10%)	6 (12%)	1 (4%)	0
Medication class				
ASA	33 (33%)	12 (24%)	2 (8%)	0
Clopidogrel	1 (1%)	0	0	0
Warfarin	3 (3%)	3 (6%)	0	0
ACE inhibitor	32 (32%)	16 (33%)	2 (8%)	0
ARB	16 (16%)	8 (16%)	2 (8%)	0
Beta blocker	17 (17%)	7 (14%)	1 (4%)	0
Other antihypertensives	31 (31%)	15 (31%)	4 (16%)	0
Statin	40 (40%)	13 (27%)	6 (24%)	0
Nitroglycerin	1 (1%)	0	0	0
Insulin	4 (4%)	3 (6%)	0	0

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; ASA: acetylsalicylic acid; CAD: coronary artery disease; FRS: Framingham risk score; GFR: glomerular filtration rate; IGT: impaired glucose tolerance.

Table 3: Cardiac evaluations performed in men with prostate cancer referred for androgen deprivation therapy.

Investigation	All patients ($n = 100$)	High FRS ($n = 49$)	Intermediate FRS ($n = 25$)	Low FRS ($n = 1$)
Echocardiogram	3	1 (2%)	1 (4%)	0
Exercise treadmill test	3	1	1	0
Positive for ischemia	1	0	1[†]	0
Negative for ischemia	2	1	0	0
Myocardial perfusion imaging	2	0	0	0
Positive for ischemia	1	0	0	0
Negative for ischemia	1	0	0	0
Stress echocardiogram	1	0	1	0
Positive for ischemia	0	0	0	0
Negative for ischemia	1	0	1[†]	0
Holter monitor	1	1	0	0
Normal	1	1	0	0
Abnormal	0	0	0	0

FRS: Framingham risk score.
[†]One patient had evidence of ischemia on exercise treadmill testing and was subsequently referred for stress echocardiogram which showed no ischemia.

been observed among men with established coronary artery disease [19]. Men with metabolic syndrome and hypertension are also at increased risk of biochemical recurrence following radical prostatectomy for prostate cancer [20–22]. Although the pathways by which the metabolic syndrome and its components increase cancer risk have not been fully elucidated, likely mechanisms involve insulin resistance, hyperinsulinemia, and elevated levels of insulin-like growth factor (IGF)-1, as well as increased levels of inflammation [17]. It is, therefore, somewhat surprising that diabetes, a state

associated with insulin resistance, was not more prevalent in our cohort than in the general population. However, this finding was consistent with previous studies and it has been suggested that this may be because advanced diabetes is associated with low insulin levels due to pancreatic β-cell failure, resulting in a late protective effect [21].

ADT has been associated with worsening cardiovascular risk profiles and with major adverse cardiac events. Men taking ADT for prostate cancer have an increased risk of obesity, insulin resistance, and dyslipidemia [23]. Although a large meta-analysis of randomized controlled trials failed to demonstrate an increased risk of cardiovascular death among men randomized to ADT [24], several retrospective analyses of ADT in nontrial settings have found increased risks of fatal and nonfatal cardiovascular events, including myocardial infarction, stroke, and peripheral arterial disease [25, 26]. The use of this therapy in men with preexisting cardiovascular disease is associated with a particularly high risk of events [27–29]. In our cohort, this accounted for 25% of the study population.

An earlier study done at our centre found that men receiving ADT had a lower prevalence of cardiovascular disease and risk factors than men who did not receive ADT [30], suggesting that this therapy was being withheld from the highest risk patients, thereby identifying a significant treatment bias. Indeed, men with prostate cancer are twice as likely to die of cardiovascular disease as they are to die of prostate cancer [31]; cardiovascular disease is the leading cause of death in this population. This therefore represents a vulnerable population in whom effective interventions for the primary and secondary prevention of cardiovascular disease are likely to be of high yield. Patients receiving ADT, in whom the risk is expected to further increase with cancer treatment, warrant particular attention in order to minimize iatrogenic escalation of cardiovascular risk. Conversely, effective modification of cardiovascular risk factors to achieve guideline-recommended targets may result in a greater proportion of prostate cancer patients being deemed eligible for ADT, resulting in improved oncologic outcomes.

In our study cohort, large proportions of patients had not had blood pressure or lipid measurements done prior to initiation of ADT. Current European Association of Urology guidelines recommend that existing general population screening and treatment strategies should be applied to patients receiving ADT [32]. Canadian Cardiovascular Society guidelines recommend annual screening of lipids for individuals with calculated Framingham risks of ≥5% [33], and the Canadian Hypertension Education Program recommends that all adults should be screened for hypertension at all appropriate visits [34]. These guidelines have also addressed pharmacologic and nonpharmacologic strategies for risk factor modification. While management of these risk factors may fall outside the scope of typical oncology practice, cardiooncology clinics can offer multidisciplinary approaches to risk reduction. Cardiooncology clinics focus on prevention and management of cardiovascular disease in cancer patients and aim to remove cardiovascular disease as a barrier to effective cancer treatment [35]. An important aspect of this care is the management of cardiovascular risk factors. In addition, supervised exercise programs offer additional opportunities for risk reduction through physical activity and have been shown to improve cardiovascular risk profiles and cardiopulmonary fitness in prostate cancer patients [36–38].

Very few patients in our cohort had undergone any form of diagnostic testing for CAD. Although the resting ECG is an insensitive method of screening for silent CAD, abnormalities including Q-waves, ST segment depression, and bundle branch block have reported specificities of >95% for the prediction of cardiovascular mortality [39]. In our cohort, 37% of ECGs performed were abnormal, reflecting the higher prevalence of cardiovascular disease in our study cohort than in the population-based cohorts from which sensitivity and specificity analyses are derived [40]. Resting ECG may therefore be a useful screening test in this high-risk population.

Exercise stress testing is a far more sensitive method of screening for CAD than resting electrocardiography. Henriksson and Johansson reported that ischemic changes during an exercise stress test, in conjunction with abnormalities of blood lipids and hormone levels, were strongly predictive of cardiovascular events among men receiving estrogen therapy for prostate cancer [41]. To our knowledge, a similar study has not been performed in men receiving ADT, but the predictive value of exercise testing in the general population has been validated and is widely accepted [42]. Moreover, Wall and colleagues have reported that maximal exercise testing is feasible and safe in men receiving ADT for prostate cancer and have emphasized the importance of exercise testing among men receiving ADT in the context of additional risk factors who are embarking on an exercise program [43].

A strength of our study was the detailed chart review methodology, likely yielding a higher prevalence of comorbidities and higher rate of cardiac testing than would have been achievable with administrative data or with self-report. There are also limitations to our study. Our sample size was relatively small, potentially limiting the precision of our results. However, we included all patients meeting our inclusion criteria over an entire year and we believe that our sample was representative of the population seen at our centre. In addition, as ADT may be withheld from patients at the highest risk for cardiovascular complications, our results cannot be generalized to all prostate cancer patients. As discussed above, we have reason to believe that the broader prostate cancer population carries, if anything, a greater risk than our cohort [30]. For comparison purposes, we were only able to obtain local population data on the prevalence of hypertension and diabetes, and we were therefore unable to compare the prevalence of cardiovascular disease or dyslipidemia in our cohort to the general population. Our findings, however, were consistent with other epidemiologic studies that have identified associations between cardiovascular risk factors and prostate cancer risk, and the fact that we were able to illustrate the increased prevalence of even a single risk factor highlights the increased risk that may be present in this population. Finally, many of our subjects were missing the necessary data to accurately calculate an FRS. However, our use of zero scores for missing data points has resulted in a

"minimal estimate" of risk, so we may be confident that we have not overestimated the risk of our cohort.

In conclusion, the results of the present study indicate that despite a low overall comorbidity burden, established cardiovascular disease and cardiovascular risk factors are common among men receiving ADT for intermediate- and high-risk localized prostate cancer. Certain risk factors are more common among prostate cancer patients referred for ADT than among population controls, possibly reflecting the fact that many cardiovascular risk factors are associated with increased prostate cancer risk and highlighting the particularly high-risk nature of this population. Moreover, our findings suggest that suboptimal risk stratification occurs in this population, and accordingly, suboptimal risk modification may result. As cardiovascular disease is a leading cause of death in men with prostate cancer and given that ADT is associated with increased risk of fatal and nonfatal cardiovascular events, this population is likely to benefit from aggressive primary and secondary prevention therapies. The findings of the present study identify an important care gap and an opportunity to improve survivorship care in this population. We propose that care processes to identify at-risk individuals, including standard cardiovascular risk factor assessment and modification or referral to a cardiologyoncology clinic where available, be broadly applied to this patient population to improve patient specific cardiac and cancer related outcomes.

Disclosure

Tom Pickles has a consultant or advisory role with Astellas Pharma and has received honoraria from Abbott Labs, Ferring Pharma, and Janssen.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Research Article

An International Survey of Health Care Providers Involved in the Management of Cancer Patients Exposed to Cardiotoxic Therapy

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Cardiotoxicity is the second leading cause of morbidity and mortality in cancer survivors. The objective of this international cardiac oncology survey was to gain a better understanding of current knowledge and practice patterns among HCPs involved in the management of cancer patients exposed to potentially cardiotoxic drugs. Between 2012 and 2013, we conducted an email-based survey of HCPs involved in the management of cardiac disease in cancer patients. 393 survey responses were received, of which 77 were from Canadian respondents. The majority of respondents were cardiologists (47%), followed closely by medical oncologists. The majority of respondents agreed that cardiac issues are important to cancer patients (97%). However, only 36% of total respondents agreed with an accepted definition of cardiotoxicity. While 78% of respondents felt that cardiac medications are protective during active cancer treatment, only 51% would consider prescribing these medications up-front in cancer patients. Although results confirm a high level of concern for cardiac safety, there continues to be a lack of consensus on the definition of cardiotoxicity and a discrepancy in clinical practice between cardiologists and oncologists. These differences in opinion require resolution through more effective research collaboration and formulation of evidence-based guidelines.

1. Introduction

Patients diagnosed with cancer today have improved five-year relative survival compared to just over a decade ago [1]. Treatment advances, including the introduction of targeted agents, continue to improve cancer survival. However, it is increasingly evident that targeted agents used in cancer therapy may negatively impact cardiovascular health [2].

Currently, cardiotoxicity is the second leading cause of morbidity and mortality in cancer survivors [3]. This has led to increasing interest by health care providers (HCPs) in developing multidisciplinary approaches to manage these patients. However, many issues in cardiac oncology remain unresolved, including a formally accepted definition of cardiac toxicity. There are few guidelines to assist in the management of patients with or at risk of cardiac toxicity. As a result, there are major knowledge gaps with limited consensus on the approach for diagnosis, management, and monitoring of cardiotoxicity. The objective of this international cardiac oncology survey was to gain a better understanding of current knowledge and practice patterns among HCPs involved in the management of cancer patients exposed to potentially cardiotoxic drugs. Additionally, we sought to obtain a census of clinical opinions concerning emerging cardiac oncology issues. Ultimately, this information will be used to inform clinical guidelines and to better standardize the diagnosis, management, and monitoring of cardiac toxicity related to cancer therapy.

2. Methods

Between 2012 and 2013, we conducted an email-based survey of HCPs involved in the management of cardiac disease in cancer patients. HCPs were identified using email directories from the Canadian Association of Medical Oncologists (CAMO), the Canadian Cardiovascular Society (CCS), the Canadian Cardiac Oncology Network (CCON), and the International Cardioncology Society (ICOS). The survey consisted of 14 base questions for international participants (ICOS) and an additional 30 questions for Canadian participants (CCON) related to cancer treatment-induced cardiotoxicity. The ICOS and CCON questionnaires were initially prepared and administered separately; the results were subsequently combined and analyzed together for this study. Questions contained multiple-choice options; some follow-up questions also allowed further elaboration. In addition to a series of short-stem questions, the CCON survey also contained two questions pertaining to a clinical case study. The case study described a 50-year-old female receiving trastuzumab for HER2 positive metastatic breast cancer. Her left ventricular ejection fraction (LVEF) at baseline was 55% but on repeat echocardiogram decreased to 30% with no cardiac symptoms. Respondents were asked to recommend further clinical management. A follow-up scenario was also included, where trastuzumab therapy was discontinued, and an angiotensin converting enzyme (ACE) inhibitor was initiated. Serial echocardiograms revealed an unchanged LVEF at 30%. The patient had no cardiac symptoms; however she was developing progressive metastatic disease. Respondents were again asked to recommend appropriate management.

The survey was developed and administered via the FLUIDS online system. A modified Dillman Total Design Survey Method was used to ensure maximal responses [4]. Descriptive data was collected and summarized.

3. Results

A total of 393 survey responses were received, of which 77 were from Canadian respondents. The majority of ICOS survey respondents were from the USA; there were also several respondents from Australia, Denmark, and Switzerland. The overall response rate was 25%. The majority of respondents were cardiologists (185/393, 47%), followed closely by medical oncologists (158/393, 40%) (Table 1). Overall, 55% of respondents were in academic practice (212/383). When considering the Canadian (CCON) respondents alone, the majority (66/77, 89%) were in academic practice. Thirty-five percent of respondents (26/77) had been practising for less than five years. Fifty-two percent (40/77) indicated that they had a dedicated cardiac oncology centre at their institution.

The majority of respondents agreed that cardiac issues are important to cancer patients (381/393, 97%). Ninety-four percent felt that the diagnosis of cardiac disease had an impact on cancer prognosis (349/383) and 77% agreed that chemotherapy or radiation is an important risk factor for cardiac disease (301/393). However, only 36% of total respondents agreed with an accepted definition of cardiotoxicity (109/383). The majority of Canadian cardiologists felt that there is no formal definition of cardiotoxicity, while the majority of Canadian oncologists felt that there was an established definition (Figure 1). In spite of the high percentage (78%) of respondents who felt that cardiac medications are protective during active treatment (307/393), only 51% would consider prescribing these medications upfront in cancer patients (199/393). A large percentage of Canadian respondents answered "not sure" (29/77, 38%) to the protective effect of cardiac medications (Figure 2) and "not sure" (25/77, 32%) as to whether they would use them in clinical practice (Figure 3).

Referring to the clinical case study of the patient with decreased LVEF, the HCPs were asked "What would be your management of her trastuzumab therapy at this time?" Twenty percent of cardiologists chose the response "discontinue trastuzumab permanently," while only 7% of oncologists chose this response. However, the response "discontinue trastuzumab, resume if EF normalizes" was chosen by 74% of

Table 1: CCON and ICOS demographics.

Demographic	$N = 393$	%
Medical specialty		
Cardiology	185	47
Medical oncology	158	40
Other	50	13
Practice setting		
Academic	212	54
Community	114	29
Other	67	17

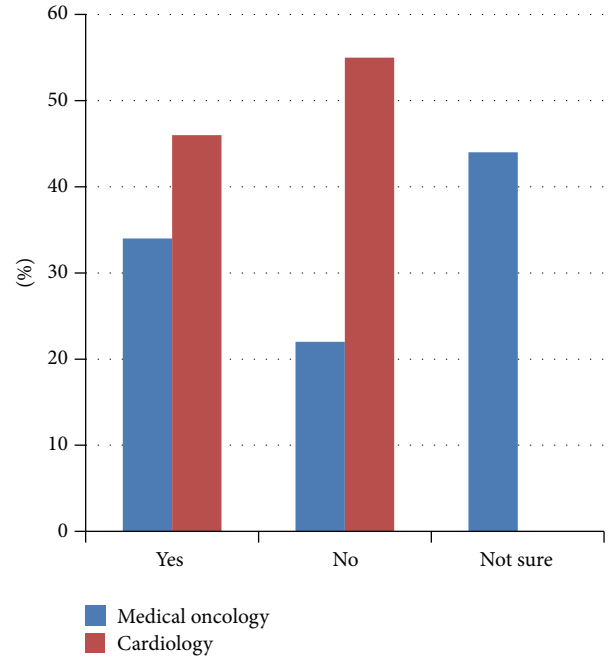

Figure 1: Is there a definition for "cardiac toxicity"? CCON results ($n = 77$).

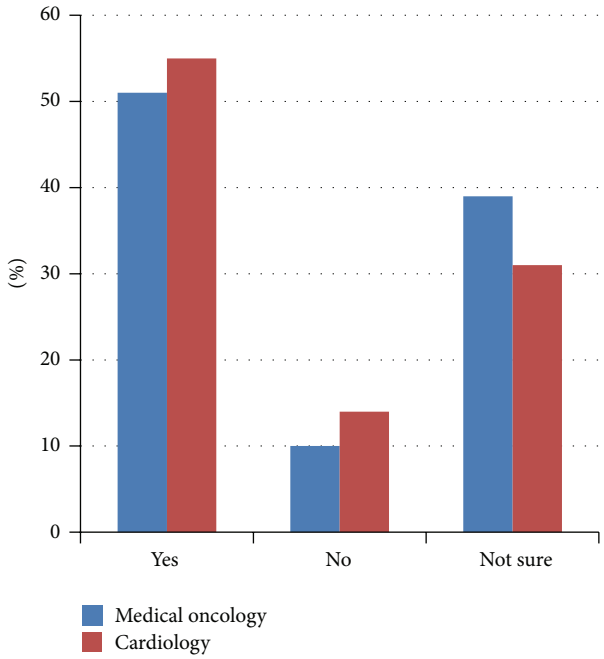

Figure 2: Are cardiac medications protective during active treatment? CCON results ($n = 77$).

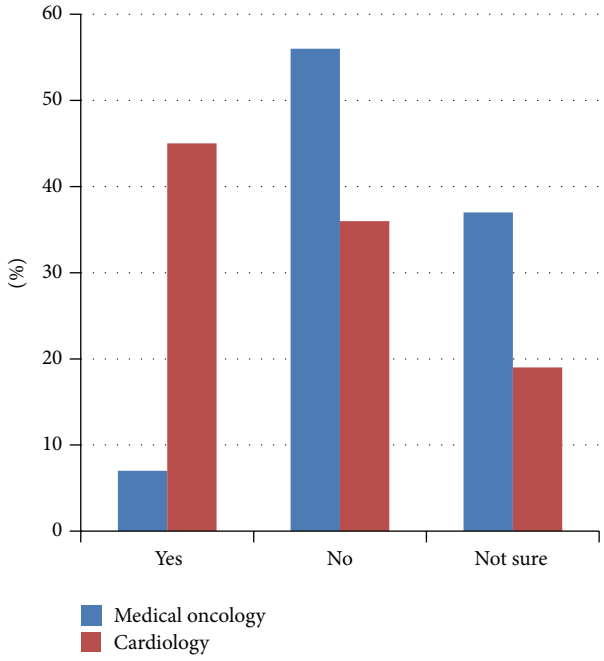

Figure 3: Would you prescribe cardiac medications to protect the heart during active cancer therapy? CCON results ($n = 77$).

oncologists, but by only 48% of cardiologists. In the follow-up question of unchanged LVEF in the presence of cancer progression, HCPs were asked "What management would you now recommend?" The results were scattered between the seven available options. The option "optimize ACE inhibitor, add beta blocker" was chosen by 52% of cardiologists and 22% of oncologists. The option "resume trastuzumab at reduced dose with serial EF" was chosen by 24% of cardiologists and 4% of oncologists. The option "other" was selected by 20% of cardiologists and 41% of oncologists.

4. Discussion

This international cardiac oncology survey was conducted to gain a better understanding of the knowledge base and clinical opinions of HCPs involved in the treatment of cancer patients being treated with potentially cardiotoxic therapy. To our knowledge, this is the first study of this kind in the field of cardiac oncology and highlights many controversial clinical issues within the field. The results affirm that opinions differ between cardiologists and oncologists regarding a formal definition of cardiotoxicity, as well as the diagnosis, management, and monitoring of oncology patients at risk of cardiovascular complications. At this time, there is no clear agreement in the literature on the definition of cancer therapy-related cardiotoxicity, and several historical definitions are in common use [5]. Recent consensus guidelines have recently been proposed in an attempt to clarify definitions; however it will take time to incorporate these recommendations into clinical practice [6]. Our results underscore the need for further collaboration between cardiologists and oncologists. Additionally, this survey demonstrated that there is a clear knowledge gap between cardiologists and oncologists in the appropriate clinical management of cancer patients who develop cardiotoxicity secondary to their cancer treatment. In the presented case study, more oncologists chose the evidence-based option [7] to "discontinue trastuzumab, resume if EF normalizes." More concerning is that almost half (48%) of the cardiologists would not suggest resuming trastuzumab in these patients even with the normalization of their LVEF, thus depriving these patients of potentially lifesaving therapy.

The clinical opinions of the majority of respondents in this survey are supported by the available literature. The small percentage of respondents who felt that there is an established definition of cardiotoxicity (36%) is in agreement with work published by Albini and colleagues [8]. The finding that the majority of respondents agreed that chemotherapy or radiation is an important risk factor for cardiac disease is consistent with the conclusion by Suter and Ewer [9] that cancer treatments may induce cardiac dysfunction (7–34%), heart failure (1–4%), and arterial hypertension (up to 23%). Nearly four-fifths of respondents felt that cardiac medications may be protective during active treatment. Previous work by Yeh and colleagues reported that cardiac medications, such as ACE inhibitors and beta blockers, may be effective in patients being treated for cancer [10].

This study has several limitations. First, we were unable to compare results with other studies, as this survey was the first of its kind in cardiac oncology. Despite use of the modified Dillman Total Design Survey Method, only one-quarter of survey recipients responded. Response rates may be improved with use of personalized correspondence and monetary or unconditional incentives such as gift certificates [11].

The underlying reasons for survey nonresponse remain unclear and may contribute to nonresponse bias [12]. It is possible that nonresponding HCPs may not consider cardiac issues to be important in cancer treatment. Respondents were likely a highly selected sample of HCPs, since over half (52%, 40/77) indicated that they had access to a dedicated cardiac oncology clinic at their institution. Multiple iterations of this survey should be conducted to further validate the findings.

Second, the survey design forced respondents to select answers in a multiple-choice format, and respondents were limited to the choices provided. Furthermore, the order of the questions might affect the responses given. Some of the questions allowed for elaboration with free text, but these were not included in the analysis because the responses were so variable. Additionally, the ICOS and CCON groups were provided with separate surveys. Retrospectively combining these surveys proved difficult and limited the uniformity of results. For future investigations, all participants should be given a uniform survey over the same time period.

Cardiac oncology is a rapidly emerging but relatively new area of clinical medicine. It is encouraging to find a high level of concern for cardiac safety among health care providers treating cancer patients. Strikingly, there continues to be a lack of consensus on the definition of cardiotoxicity and a discrepancy in clinical practice between cardiologists and oncologists, the two specialties mostly involved in caring for cardiac oncology patients. These differences in opinion will need to be resolved through more effective research collaboration, formulation of evidence-based guidelines, and educational strategies to standardize the diagnosis, management, and monitoring of cardiac toxicity.

Appendix

See Table 1.

Conflict of Interests

The authors report no conflict of interests.

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Review Article

Multimodality Imaging in Cardiooncology

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Cardiotoxicity represents a rising problem influencing prognosis and quality of life of chemotherapy-treated patients. Anthracyclines and trastuzumab are the drugs most commonly associated with development of a cardiotoxic effect. Heart failure, myocardial ischemia, hypertension, myocarditis, and thrombosis are typical manifestation of cardiotoxicity by chemotherapeutic agents. Diagnosis and monitoring of cardiac side-effects of cancer treatment is of paramount importance. Echocardiography and nuclear medicine methods are widely used in clinical practice and left ventricular ejection fraction is the most important parameter to asses myocardial damage secondary to chemotherapy. However, left ventricular ejection decrease is a delayed phenomenon, occurring after a long stage of silent myocardial damage that classic imaging methods are not able to detect. New imaging techniques including three-dimensional echocardiography, speckle tracking echocardiography, and cardiac magnetic resonance have demonstrated high sensitivity in detecting the earliest alteration of left ventricular function associated with future development of chemotherapy-induced cardiomyopathy. Early diagnosis of cardiac involvement in cancer patients can allow for timely and adequate treatment management and the introduction of cardioprotective strategies.

1. Introduction

Chemotherapy is widely used in the treatment of several neoplastic diseases, leading to an improvement in survival and prognosis in a large number of patients. Side effects are the most common cause of restriction to its use. Cardiotoxicity represents a frequent complication secondary to the intake of some classes of chemotherapeutic agents, with significant consequences on patients' outcome [1]. Heart failure (HF) is the most common manifestation of chemotherapy induced cardiotoxicity. Although left ventricular ejection fraction (LVEF) is widely utilized in monitoring the cardiac function in clinical practice, it has not demonstrated high sensitivity in detecting subclinical myocardial dysfunction. New parameters and new imaging techniques have been developed in order to overcome the limitations related to isolate evaluation of LVEF [2, 3]. A diagnostic approach based on the integrative use of different imaging techniques can allow early detection of cardiotoxicity, improving the therapeutic management of the neoplastic disease, quality of life, and mortality rate.

2. Clinical Manifestations of Cardiotoxicity

HF occurs with an incidence range included between 0.5 and 28%, depending on the medication used, and is the most common clinical manifestation of the cardiotoxicity induced by chemotherapy [1]. The onset of dyspnea, chest pain, peripheral edema, and asthenia is usually preceded by a variable stage of subclinical myocardial dysfunction. Traditionally cardiotoxicity induced by chemotherapy has been classified into two groups [4]: Type I chemotherapy-related myocardial dysfunction is typical of anthracyclines and has been related to oxidative stress causing myocardiocytes damage and death; it is an irreversible, dose-dependent

process and is characterized by ultrastructural alteration identifiable by myocardial biopsy. Type II chemotherapy-related myocardial dysfunction is induced by trastuzumab and is related to the inhibition of ErbB2 pathway. Usually the dysfunction is reversible and not related to the cumulative dose [5].

Coronary artery disease, presenting with asymptomatic T-wave changes, chest pain, acute coronary syndromes, and myocardial infarction, is mainly related to use of antimetabolites (particularly 5-fluorouracil). De Forni reported an incidence of acute coronary syndromes of about 7.6% in patients treated with 5-fluorouracil while cardiac mortality reached 2.2% [6].

Hypertension is a relatively common side effect of several antiangiogenetic drugs like bevacizumab, sunitinib, and sorafenib. Underlying artery hypertension is the most important risk factor for the development of the secondary disease.

Cancer patients have a high incidence of thromboembolic events depending on cancer-related factors (primitive malignancy localization, immobility, HF, arrhythmias, etc.) [7] and additional effects of some chemotherapeutic agents, particularly, cisplatin and thalidomide [8, 9].

3. Cancer Treatment and Cardiotoxicity: Who Are the Actors?

The majority of studies on cardiotoxicity focus on patients treated with anthracyclines and trastuzumab. Anthracyclines (doxorubicin, daunorubicin, and epirubicin) use has been related to onset of HF within 1 year in about 2% of treated patients [1]. The HF incidence increases to 28% when the patients are exposed to the association of anthracyclines and trastuzumab [1]. Cardiotoxic effect has been described for classes of drugs other than the anthracyclines and trastuzumab such as inhibitors of tyrosine kinases (imatinib, dasatinib, nilotinib, sunitinib, sorafenib, and bevacizumab), antimetabolites (5-fluorouracil), alkylating agents (cisplatin, cyclophosphamide), and taxanes (docetaxel and paclitaxel) [10]. Radiotherapy has become an important instrument in the treatment of several malignances and is more often associated to standard chemotherapy treatment. Irradiation of the mediastinum with a cumulative dose >30 Gy and a daily fractioning >2 Gy appeared to be related to a high risk of developing cardiac dysfunction [11].

4. How to Diagnose Cardiotoxicity? The Need for Multimodality Imaging

Myocardial biopsy is still considered the most accurate and specific method in identifying the myocardial damage induced by chemotherapy, detecting the ultrastructural alteration of cardiomyocytes [12]. Nevertheless its invasiveness limited its use in clinical practice. Imaging methods emerged in the last decades as the landmark in monitoring cardiotoxicity in cancer patients. Left ventricular ejection fraction (LVEF) is widely considered the most important parameter for the diagnosis of cardiotoxicity. The most validated definition of cardiotoxicity has been established by the cardiac review and evaluation committee [13]. Cardiotoxicity can be defined either by the onset of HF symptoms and signs or by an asymptomatic decrease of LVEF as follows.

Cardiac Review and Evaluation Committee Criteria for Diagnosis of Cardiotoxicity. The diagnosis of cardiotoxicity is established if one or more criteria are present:

> cardiomyopathy characterized by a decrease in cardiac LVEF that was either global or more severe in the septum,
>
> symptoms of congestive heart failure,
>
> associated signs of congestive heart failure, including but not limited to third heart sound (S3) gallop, tachycardia, or both,
>
> decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of congestive heart failure,
>
> decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms.

Although the evolution of most recent imaging techniques has allowed accurate and reproducible evaluation of volumes and of alteration of LVEF, recently it has appeared evident that the drop of LVEF represents a late phenomenon in the physiopathology of the chemotherapy-induced cardiotoxicity. This evidence has led the clinicians to look to other imaging methods that evaluate cardiac function independently of cardiac volumes changes, aiming to detect the earliest manifestation of cardiotoxicity and allowing for the appropriate management of the therapy. Some of these methods such as speckle tracking imaging have been already introduced in clinical practice whereas others are under investigation in experimental settings.

5. Methods Based on the Evaluation of LVEF: From Echocardiography to Cardiac Magnetic Resonance

5.1. Two-Dimensional Echocardiography. LVEF evaluated by two-dimensional echocardiography (2DE) is the most used parameter in monitoring the cardiac func-tion in chemotherapy-treated patients (Videos 1 and 2; see Supplementary Material available online at http://dx.doi.org/10.1155/2015/263950). The Simpson biplane method is the most validated technique to obtain the left ventricle volumes, while monodimensional measurements are less accurate. However, LVEF derived by the Simpson formula relies on geometrical assumptions and the manual tracking of the endocardial border can differ when performed by different observers, particularly with poor quality images. Indeed, a recent investigation reported that 2DE is unable to estimate a decrease <10% within the 95% of confidence interval when performed by different investigators [14]; considering that cardiotoxicity has been defined as a drop of LVEF ≥10% or ≥5% in presence of HF symptoms, it is clear that the diagnosis provided by 2DE can be burdened by significant inaccuracy. Nevertheless, LVEF derived by 2DE remains the most used

method in clinical practice because of its high availability and feasibility.

5.2. Real-Time Three-Dimensional Echocardiography. Real-time three-dimensional echocardiography can obtain a full-volume scan of the left ventricle, providing a quantification of volumes independently of geometrical assumptions. LVEF provided by RT-3DE (Figure 1) demonstrated elevated correlation with the values derived by cardiac magnetic resonance as shown in a study on 50 patients where Walker reported a correlation ranging from 0.90 to 0.97, while 2DE revealed a weak correlation (from 0.31 to 0.53) [15]. LVEF derived by RT-3DE showed the lower intraobserver and interobserver variability (0.017 and 0.027, resp.) and the best minimal detectable variation (4.8% intraobserver and 7.5% interobserver) [14].

5.3. Contrast Echocardiography. The accuracy in the measurement of volumes and LVEF is affected negatively by the poor quality of the acoustic window, which often limits the adequate visualization of the endocardial border. Use of contrast echocardiography demonstrated an incremental value, reducing the interobserver variability in evaluating the cardiac volumes and wall motion score index [16]. Use of contrast associated with 2DE resulted in a reduction of the interreader variability of LVEF from 14.3% (95% confidence interval, 11.7%–16.8%) to 8% (95% CI, 6.3%–9.7%; $P < 0.001$) [17]. Left ventricle opacization is recommended when two or more segments are not well visualized [18, 19]. The value of contrast administration with RT-3DE is uncertain; Hoffmann demonstrated a reduction of interobserver variability from 14.3% to 7.4% [17], while Thavendiranathan did not report any incremental value in comparison to noncontrast RT-3DE [14].

5.4. Nuclear Medicine Imaging. In the past, MUGA has been the most common alternative to echocardiography in the evaluation of chemotherapy-treated patients [20]. MUGA makes use of 99mTC-erythrocyte labeling enabling the visualization of the cardiac blood pool by γ-camera with electrocardiogram-triggered acquisitions. The final result provides a highly reproducible and precise quantification of LV volumes and dyssynchrony independently of geometrical assumption [21]. LVEF values provided by MUGA demonstrated reproducibility and sensitivity comparable to 3D echocardiography and CMR. Walker reported a correlation between LVEF evaluated by MUGA and CMR ranging from 0.87 to 0.97 [15]. Nevertheless, now MUGA is rarely used in clinical practice mainly because of the increased radiation exposure for patients and the introduction of new noninvasive techniques such as CMR and RT-3DE.

5.5. Cardiac Magnetic Resonance (CMR). In the last years, CMR has emerged as the criterion standard technique in the evaluation of LV mass [22] and volumes. It provides a modeling of the cardiac chambers free from geometric assumptions and independently of acoustic window, providing the most accurate evaluation of global and regional myocardial dysfunction [23]. Armstrong demonstrated a decrease of LVEF and mass in a population of asymptomatic adult survivors of childhood cancer treated with anthracyclines in which other imaging techniques did not detect alterations [24] and similar findings have been reported by Ylänen [25]. CMR is indicated for the evaluation of patients treated with potentially cardiotoxic medications as an alternative to 2DE, particularly in patients with an echocardiographic cardiotoxicity diagnosis in whom the interruption of treatment could be inadvisable or in patients with poor echocardiographic images [26]. Although it has advantages, CMR usage is limited by its low availability and elevated cost. The method is not indicated in patients with metallic prosthesis, and the results are less accurate in subjects with arrhythmias.

6. New Methods and Strategies to Monitor Cardiac Function Independently of LVEF: Clinical Practice and Future Insights

6.1. 2DE and Tissue Doppler Imaging (TDI). Alteration of diastolic function precedes the systolic dysfunction often representing the first sign of early cardiac dysfunction caused by anticancer agents [27]. 2DE is the best method for the evaluation of diastole. The decrease of the early to late ventricular filling velocities (E/A) ratio, the enlargement of the left atrium, and the increase of isovolumic relaxation time are common findings in chemotherapy-treated patients [28, 29] with impairment of diastolic function as well as reduction of E^1/A^1 ratio [5, 30, 31] and the increase of E/E^1 ratio >10 [28]. Although the diastolic dysfunction is frequent in chemotherapy-treated patients, its value in predicting the late development of cardiotoxicity is affected by many factors, such as aging, hypertension, and load conditions. Some authors reported that E, E^1, E/A, and isovolumic relaxation time did not predict late LVEF <50% within three years after the start of treatment [32]. Analysis of systolic function performed by TDI provided contrasting results: in a study by Fallah-Rad 42 patients demonstrated a significant reduction of lateral S^1 within three months from the start of chemotherapy. The decrease was ≥0.6 cm/s in all 10 patients who later developed LVD [33]. However, the result of the study was limited by several biases: above all, there was a high incidence of cardiotoxicity in a relatively small and young population. In effect, other studies failed in revealing a significant reduction of S' in chemotherapy-treated patients [34, 35]. Myocardial deformation analysis derived from TDI demonstrated early alteration of both systolic and diastolic function after chemotherapy [36, 37]. Nevertheless, TDI measurements suffer from angle dependence, noise, translational movements, aliasing, and reverberation. For these reasons, myocardial deformation analysis derived by TDI has been almost totally replaced by speckle tracking echocardiography.

6.2. Two-Dimensional Speckle Tracking Echocardiography. Two-dimensional speckle tracking echocardiography (2D-STE) analyzes the myocardial deformation on two-dimensional images by tracking natural acoustic reflections and interference patterns, called "speckle." The software is able to provide the percentage of distance variation (deformation)

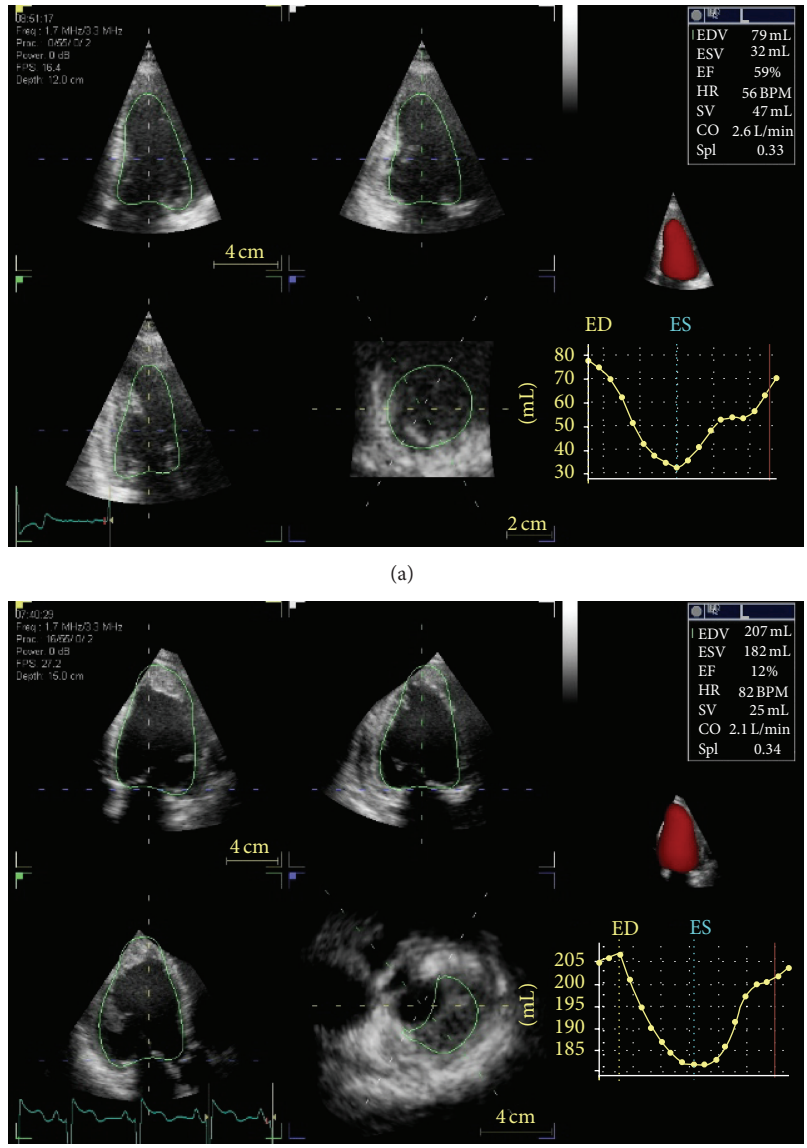

Figure 1: Three-dimensional echocardiography: evaluation of left ventricular ejection fraction in a normal patient (a) and in one with impaired function (b).

between speckles within a predefined region of interest, obtaining a value defined as "strain." The velocity of the deformation is defined "strain rate." 2D-STE provides an accurate definition of longitudinal, circumferential, and radial component of the ventricular deformation. Twist, untwist, and torsion are additional parameters that evaluate the torsional deformation of the left ventricle. Strain evaluated by 2D-STE detected early myocardial dysfunction in chemotherapy-treated patients [38, 39] (Figure 2 and Videos 3 and 4). The application of strain and strain rate to cardiotoxicity detection has been evaluated in several relatively small studies. Global longitudinal strain (GLS) appears to be the most sensitive parameter of deformation for the detection of early systolic dysfunction. Negishi demonstrated that, in 81 patients treated for breast cancer, GLS rate and early diastolic strain rate were significantly decreased at 6 months from treatment, in comparison to baseline value in 30% of patients who developed cardiotoxicity at 12 months. GLS percentage variation was the strongest predictor of cardiotoxicity (area under the curve, 0.84) and a reduction >11% was the optimal cut-off (sensitiveness 65%, specificity 94%) [40]. Similar results have been reported by Plana showing that a decrease of >9% in GLS after the third cycle of epirubicin was the best independent and accurate predictor of cardiotoxicity (sensitiveness 84%, specificity 80%; $P = 0.0001$) in a sample of cancer treated patients [26]. Stoodley showed a correlation between reduction of GLS and cumulative dose of anthracyclines [41]. Thavendiranathan [42] collected the fragmentary data from several studies and reported the results in a comprehensive, systematic review.

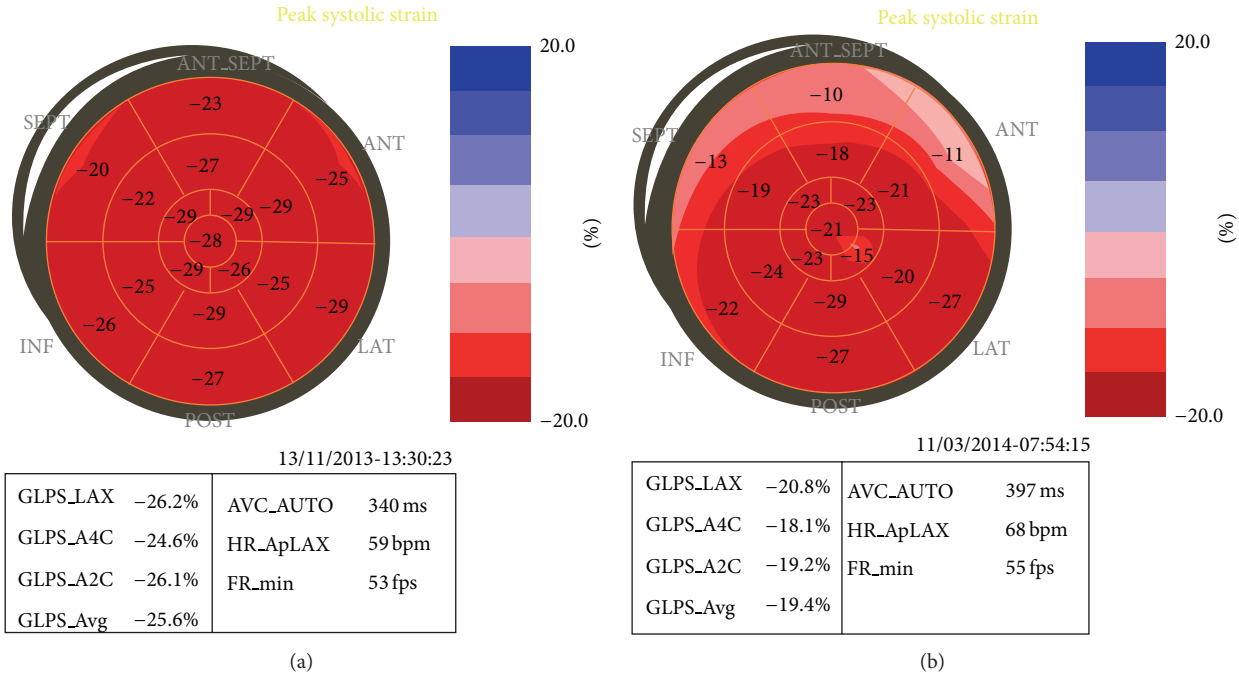

Figure 2: Bull's eyes showing a decrease of global and regional strain in a patient before (a) and after (b) treatment with chemotherapy. In the same patient the left ventricular ejection fraction was not significantly altered (see also Supplementary Videos 3 and 4).

The authors established that the percentage of change is a better indicator than a defined cut-off because of the variable baseline values. A variation in GLS ranging from 10% to 15% was the best predictor of future development of cardiotoxicity. Negishi established in 81 women treated with trastuzumab that GLS decrease can predict cardiotoxicity and an 11% reduction was the optimal cut-off (confidence interval 8.3%–14.6%) [40]. According to these findings, the recent consensus document released by the American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) defined that a variation in GLS >15% is strongly predictive of future development of cardiotoxicity, while a variation <8% is not significant [26]. An important limitation associated with the use of STE is represented by differences in the deformation values provided by software from different vendors [43]. Waiting for a full standardization of the measurement, the recommendation is to evaluate the patients with the same software during the follow-up.

6.3. Three-Dimensional Speckle Tracking Echocardiography. Three-dimensional speckle tracking echocardiography (3D-STE) is one of the most advanced techniques in the evaluation of myocardial deformation. The possibility of evaluating the deformation on a full-volume model avoids the errors derived from the use of two-dimensional images. Xu compared 3D-STE to 2D-STE and revealed that GLS evaluation is slightly less feasible in comparison to 2D-STE (84.9% versus 97.2%); however, 3D-STE appeared less time-consuming (50.5 ± 6.4 sec versus 68.0 ± 9.2 sec) and the correlation was good between values obtained by the two methods appearing to be larger for structural measurements rather than for deformation analysis. Inter- and intraobserver variability ranged from 4.8% to 7.9% [44]. Yu demonstrated that childhood cancer survivors evaluated by 3D-STE had significantly reduced GLS and torsion ($P < 0.001$) and greater systolic dyssynchrony index in comparison to healthy controls [45]. Mornoş found that GLS evaluated by 3D-STE was superior to biomarkers and to LVEF in predicting future development of cardiotoxicity [46]. Although 3D-STE is a promising method, the studies which compared the technique to the other standard methods are few and included a small number of patients. A clear superiority to 2D-STE in predicting development of future cardiotoxicity has not yet been evaluated. Moreover, 3D-STE is not widely available in the echo-labs; thus its use, so far, has to be considered experimental.

6.4. Stress Echocardiography. Stress-echocardiography revealed contrasting results in the evaluation of chemotherapy-treated patients: some studies report a reduction of LVEF during stress in patients treated with chemotherapy in comparison to controls [47], while other studies did not report any incremental value of the technique [48, 49]. The only use of stress echocardiography is the evaluation of inducible ischemia in patients with high or intermediate pretest probability for coronary artery disease treated with drugs associated with ischemia (fluorouracil, bevacizumab, sorafenib, and sunitinib) [50].

6.5. Cardiac Magnetic Resonance. A good incremental value provided by CMR relies on the possibility of the method to perform a tissue characterization, identifying fibrosis and edema. The use of this technique can be used to investigate

both early and late myocardial dysfunction in chemotherapy-treated patients.

6.5.1. Detection of Early Cardiotoxicity. Preliminary human studies using T2 weighted sequences showed a significant increase of signal intensity after three days of therapy; this finding is indicative of interstitial edema and was predictive of LVEF reduction at 1 year [51]. A study of 22 patients receiving anthracyclines showed that, after three days of treatment, an increase >5 times of the ratio between signal intensity pre- and postcontrast administration was predictive of reduction of LVEF at 28 days and six months [52]. Delayed enhancement (DE) consists of the acquisition of delayed sequences after administration of gadolinium, which detects tissue with slow contrast washout, usually represented by scar or fibrosis. Fallah-Rad revealed subepicardial linear DE in the lateral wall of LV in all 10 patients with trastuzumab-induced cardiomyopathy even though, in only 40% of cases, DE during therapy was predictive of subsequent decline of LVEF [53]. A contrasting result has been recently presented by Drafts; the authors reported absence of DE during follow-up of anthracycline-treated patients, despite a significant decrease in LVEF [54].

6.5.2. Detection of Late Cardiotoxicity. The improvement of cancer therapy has led to longer survival; accordingly, late cardiotoxic effects of chemotherapy have been observed in many patients. Reduction of LV mass has been evaluated as a marker of late cardiotoxicity. A sample of childhood cancer survivors presented LV mass <2 standard deviation (SD) of the mean value for normal population in 50% of cases [24]. A study carried out by Neilan to evaluate the prognostic value of CMR in adult patients revealed that LV mass index was an independent predictor associated with major adverse cardiovascular events [55].

6.6. Nuclear Medicine Imaging. Nuclear imaging is rapidly evolving, providing new techniques with potential involvement into the evaluation of chemotherapy-treated patients. Functional imaging techniques are able to assess pathophysiologic and neurophysiologic processes at the tissue level. Metaiodobenzylguanidine (MIBG) shares the same metabolic pathway as norepinephrine; when marked with 123I, it is able to represent a scintigraphic image of the efferent sympathetic nervous innervations of the heart. A decrease in myocardial uptake is a strong predictor of mortality and cardiac death [56]. Patients treated with anthracycline in a dose-dependent way showed a quick reduction in 123I MIBG uptake, which was predictive of late cardiotoxicity [57, 58]. A specific anti-myosin antibody marked with 111In has been used to identify cardiomyocyte injury and necrosis in patients treated with anthracyclines, representing a predictor of LVEF decrease [59]. Although these new techniques are very promising for the future, at the moment, their use remains limited to an experimental setting.

7. Conclusions

Use of chemotherapy and radiotherapy is essential for cancer patients and cardiotoxicity represents one of the most frequent causes of treatment interruption with significant implications on the prognosis. Early diagnosis and detection of high risk patients has become a central issue in the management of cancer patients involving both cardiologists and oncologists. Systematic and periodical monitoring of LVEF remains the most used technique to diagnose cardiotoxicity in clinical practice. 2DE is the most used method; however, 3DE has proved to be more accurate and reproducible and is preferable if available. CMR is the criterion standard but its low availability and the high cost limit its use to particular subsets of patients (poor acoustic window or patients in whom treatment interruption is highly hazardous). Nevertheless, the decrease of LVEF occurring only in end-stage has shown that it is not suitable as an early indicator of cardiotoxicity. Among the new techniques that evaluate the cardiac function independently of the analysis of volumes and only GLS derived by 2D-STE has validated supporting evidence in predicting late cardiotoxicity. Baseline and periodical evaluation of GLS is recommended by the recent guidelines by ASE/EACVI [26]. Promising techniques such as 3D-STE and tissue characterization performed by CMR are under investigation and could provide new insights into the future for the evaluation of chemotherapy-treated patients.

Disclosure

Dr. Charles C. Bomzer discloses that he owns publicly held stock in Merck, Inc., and Pfizer, Inc.

Conflict of Interests

There are no conflicts of interest to report for any of the authors relative to this submission.

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Research Article

Clinical Experience of Patients Referred to a Multidisciplinary Cardiac Oncology Clinic: An Observational Study

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Cardiotoxicity is the second leading cause of long-term morbidity and mortality among cancer survivors. The purpose of this retrospective observational study is to report on the clinical and cardiac outcomes in patients with early stage and advanced cancer who were referred to our multidisciplinary cardiac oncology clinic (COC). A total of 428 patients were referred to the COC between October 2008 and January 2013. The median age of patients at time of cancer diagnosis was 60. Almost half of patients who received cancer therapy received first-line chemotherapy alone (169, 41.7%), of which 84 (49.7%) were exposed to anthracyclines. The most common reasons for referral to the cardiac oncology clinic were decreased LVEF (34.6%), prechemotherapy assessment (11.9%), and arrhythmia (8.4%). A total of 175 (40.9%) patients referred to the COC were treated with cardiac medications. The majority (331, 77.3%) of patients were alive as of January 2013, and 93 (21.7%) patients were deceased. Through regular review of cardiac oncology clinic referral patterns, management plans, and patient outcomes, we aim to continuously improve delivery of cardiac care to our patient population and optimize cardiac health.

1. Introduction

With the evolution of systemic and targeted therapies in cancer treatment, it has become increasingly evident that damage to the heart may occur as a result of cancer therapy. While cancer survivorship has significantly increased over the last decade [1], cardiotoxicity is the second leading cause of long-term morbidity and mortality among cancer survivors [2]. In addition, there are an increasing number of cancer patients with preexisting heart disease, for whom treatment with potentially cardiotoxic cancer therapy may pose a challenge [1]. Prevention and management strategies of cardiotoxicity will be important to optimize cancer care while maintaining cardiovascular health. Hence, the need for collaboration between oncologists and cardiologists from diagnosis to survivorship is imperative to ensure patients are receiving the best possible cancer care.

Modern cancer therapies can be complex, and their potential impact on cardiovascular health may compromise the provision of the best available cancer treatment. For patients and their families, receiving a cancer diagnosis and navigating the cancer care system poses a significant challenge. These difficulties may be compounded if cardiac complications arise from cancer therapy, and multiple medical specialties are involved in the patient's circle of care. Historically, cancer patients experiencing cardiotoxicity related to their cancer treatment have been referred to cardiologists with minimal knowledge of the importance of these cancer

therapies and their impact on cardiovascular health [3]. This has led to significant variability in the assessment and management of these patients.

Although cardiotoxicities associated with conventional chemotherapy are well known, the short- and long-term effects of targeted agents on the heart are less well understood. A growing number of targeted therapies (e.g., mTOR inhibitors, tyrosine kinase inhibitors, and VEGF inhibitors), given as single agents or in combination with systemic therapy, are being approved for use in a wide variety of malignancies. For example, agents that target angiogenesis via inhibition of vascular endothelial growth factor receptor pathways (e.g., bevacizumab, sunitinib, and sorafenib) have been shown to improve survival in patients with several solid tumours, including colorectal, renal, and hepatocellular carcinomas [4, 5]. However, the potential impact of these agents on the cardiovascular health of cancer survivors (e.g., congestive heart failure, hypertension) is less clear [6, 7]. A recent meta-analysis of 7000 patients treated with the tyrosine kinase inhibitor sunitinib demonstrated a 4.1% incidence of treatment-related heart failure [8]. A similar analysis of 900 patients treated with sorafenib observed a 1% rate of cardiac dysfunction [9]. Due to the retrospective nature of these data, more studies are required to establish a direct link, as well as investigation of other indirect effects and toxicities seen in this patient population [10].

In order to provide cancer patients with the best possible therapy without compromising cardiac health, a multidisciplinary (medical oncology, cardiology, pharmacy, and nursing) cardiac oncology clinic was established at The Ottawa Hospital in 2008—the first program of its kind in Canada [11]. The goals of the cardiac oncology clinic are to streamline referral of patients with cardiac complications related to cancer therapies; gain expertise in the management of cancer therapy–induced cardiotoxicity; provide consistent cardiac care; and further the cardiac oncology field through research and education.

The purpose of this retrospective observational study is to report on the clinical and cardiac outcomes of patients with early stage and advanced cancer who were referred to our multidisciplinary cardiac oncology clinic. This study was approved by the Ottawa Hospital Research Ethics Board.

2. Patients and Methods

All cancer patients (early and advanced stage) treated at the Ottawa Hospital Cancer Center and referred to the cardiac oncology clinic between October 2008 and January 2013 were eligible for this retrospective observational study. Data collection included patient demographics, cardiac risk factors, cancer treatment and completion rates, cardiac assessments (echocardiogram/MUGA) prior to and during cancer treatments, cardiac treatment, and clinical outcomes (disease progression, death). Data on cancer radiation treatments was not collected. Patients were referred to the cardiac oncology clinic by their primary oncologist if they had a LVEF <50% presystemic therapy, a decline in LVEF to <50% during treatment, a decline in LVEF by ≥10 percentage points during treatment, concerns regarding treatment-related cardiotoxicity, symptoms of other cardiac diseases (e.g., arrhythmia, pericardial disease, coronary artery disease, and valvulopathy), or evidence of symptomatic congestive heart failure. Changes in LVEF were calculated based on percentage differences from baseline assessment. MUGA scans and echocardiograms (to assess LVEF) were done in the majority of patients prior to commencing cancer therapy and as per institution policy. Additional cardiac investigations were performed at the discretion of the treating physician.

Table 1: Patient demographics ($N = 428$).

	N (%)
Median age at diagnosis	60 years (r: 18–90 years)
Gender	
(i) Female	300 (70.1%)
(ii) Male	128 (29.9%)
Primary tumour type	
(i) Breast	246 (57.5%)
(ii) Gastrointestinal	63 (14.7%)
(iii) Genitourinary	52 (12.1%)
(iv) Haematological	31 (7.2%)
(v) Lung	17 (4.0%)
(vi) Other*	19 (4.4%)
Cardiac risk factors (median)	2 (r: 0–7)
(i) Smoker	188 (43.9%)
(ii) Hypercholesterolemia	173 (40.4%)
(iii) Obesity (BMI > 30)	123 (28.7%)
(iv) Hypertension	114 (26.6%)
(v) Diabetes	57 (13.3%)
(vi) Coronary artery disease	21 (4.9%)

*Other tumour sites: gynaecologic, skin, sarcoma, neurologic, amyloidosis, thyroid, musculoskeletal.

3. Results

Between October 2008 and January 2013, 428 patients were referred to the cardiac oncology clinic. Baseline patient demographics are shown in Table 1. The median age of patients at the time of cancer diagnosis was 60 years (r: 18–90 years). The majority of patients had breast cancer (246, 57.5%), followed by gastrointestinal malignancies (63, 14.7%) and genitourinary malignancies (52, 12.1%). Less common tumour types included lung, sarcoma, thyroid, and haematological malignancies. Patients had a median of two (r: 0–7) cardiovascular risk factors at the time of referral to the cardiac oncology clinic, the most common risk factors being smoking (188, 43.9%), hypercholesterolemia (173, 40.4%), obesity (123, 28.7%), and hypertension (114, 26.6%).

The majority (405, 94.6%) of patients received cancer therapy as outlined in Table 2. First-line therapy included chemotherapy alone (169, 41.7%), targeted therapy alone (24, 5.9%; monoclonal antibodies or tyrosine kinase inhibitors), and combined therapy (163, 40.2%). Of those who received first-line chemotherapy alone, 84 (49.7%) patients were

Table 2: Cancer therapy ($N = 405$).

	N (%)
Cancer therapy	$N = 405$
(i) First-line chemotherapy alone	169 (41.7%)
(ii) First-line targeted therapy alone*	24 (5.9%)
(iii) First-line combined therapy (chemotherapy and targeted therapy)	163 (40.2%)
(iv) Second-line therapy (chemotherapy and/or targeted therapy)	128 (31.6%)
First-line chemotherapy alone	$N = 169$
(i) Anthracycline-based	84 (49.7%)
(ii) Non-anthracycline-based	85 (50.3%)
(iii) Median anthracycline dose	277 mg/m^2 (r: 46–4803)
Number of chemotherapy cycles (median)	
(i) First-line chemotherapy	6 (r: 0–59 cycles)
(ii) Second-line chemotherapy	5.5 (r: 0–33 cycles)

*Targeted therapy examples: trastuzumab, sunitinib, bevacizumab, sorafenib, and imatinib.

Table 3: Reason for referral to the cardiac oncology clinic ($N = 428$).

	N (%)
Reasons for referral	$N = 428$
(i) Decreased LVEF	148 (34.6%)
(ii) Prechemotherapy assessment	51 (11.9%)
(iii) Arrhythmia	36 (8.4%)
(iv) Congestive heart failure	24 (5.6%)
(v) Cardiomyopathy	14 (3.3%)
(vi) Other*	128 (29.9%)

*Other examples: pericardial disease, valvular heart disease, coronary artery disease, and hypertension.

Table 4: Chemotherapy outcomes ($N = 341$).

	N (%)
Completed chemotherapy	$N = 224$ (60.4%)
(i) Prior to beginning cardiac therapy	33 (14.7%)
(ii) During cardiac therapy	56 (25%)
(iii) After completing cardiac therapy	135 (60.2%)
Resumed/ongoing	12 (3.5%)
Discontinued	105 (30.8%)

Table 5: Cardiac outcomes ($N = 428$).

	N (%)
Mode of prechemotherapy LVEF assessment	$N = 381$
(i) ECHO	286 (5.1%)
(ii) MUGA	84 (22.0%)
(iii) Other/combined modalities	11 (2.9%)
(iv) Pre-chemo-LVEF (median)	60% (r: 25.0–81.2)
Change in LVEF	$N = 381$
(i) No significant decline	232 (60.9%)
(ii) Any decline	196 (51.4%)
LVEF outcome	N = 196
(i) Full recovery	55 (28.0%)
(ii) Partial recovery	16 (8.2%)
(iii) Stable	59 (30.0%)
(iv) Progressive decline	55 (28.0%)
(v) Unknown	11 (5.8%)
Cardiac medication(s)	$N = 175$
(i) ACE inhibitors	39 (22.3%)
(ii) Beta-blockers	22 (12.6%)
(iii) ACE inhibitors + beta-blockers	24 (13.7%)
(iv) Multiple	90 (51.4%)

exposed to anthracycline-based regimens. The median anthracycline exposure was 277 mg/m^2 (r: 46–4803 mg/m^2). The median number of first-line chemotherapy cycles was 6 (r: 0–59 cycles), and 128 (31.6%) patients received second-line systemic therapy (median number of cycles = 5.5 (r: 0–33 cycles)).

The most common reasons for referral to the cardiac oncology clinic were decreased left ventricular ejection fraction (LVEF) (148, 34.6%), prechemotherapy assessment (51, 11.9%), and arrhythmia (36, 8.4%). Less common reasons included angina, congestive heart failure, and cardiomyopathy (Table 3).

Chemotherapy outcomes are illustrated in Table 4. As of January 2013, the majority (224, 60.4%) of patients who received chemotherapy (341, 79.7%) successfully completed their recommended therapy. A further twelve patients (3.5%) were receiving ongoing treatment. Reasons for discontinuation of chemotherapy (105, 30.8%) varied considerably, but the majority were due to change in clinical status (e.g., disease progression). Eighty-four (19.6%) patients were receiving ongoing targeted therapy or other medications; outcome data was not available for these patients.

Cardiac outcomes are illustrated in Table 5. The majority (381, 89.0%) of patients had baseline cardiac imaging (MUGA/echocardiogram) performed prior to commencing cancer treatment. Subsequent cardiac imaging was performed at the discretion of the treating physician. A large number of patients (196, 51.4%) exhibited at least one episode of decreased LVEF from baseline. The majority (76, 38.8%)

Table 6: Patient outcomes ($N = 428$).

	N (%)
Living	331 (77.3%)
Deceased	$N = 93$ (21.7%)
(i) Progression	81 (87.1%)
(ii) Cardiac etiologies	6 (6.4%)
(iii) Other	6 (6.4%)
Lost to follow-up	4 (0.9%)

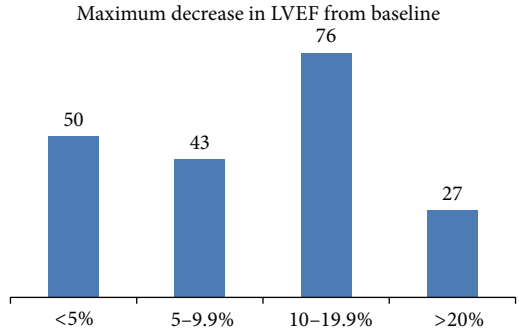

Figure 1: Maximum decrease in LVEF from baseline ($N = 196$).

of these patients exhibited a decrease between 10% and 19.9% and 27 (13.8%) patients had a decrease in LVEF of more than 20% (Figure 1). Recovery of LVEF to baseline was seen in 55 (28.0%) patients and partial recovery was recorded in a further 16 (8.2%) patients. However, further decline in LVEF occurred in 55 (28.0%) patients. A total of 59 (30.0%) patients achieved stable LVEF with cardiac intervention. A total of 175 (40.9%) patients referred to the cardiac oncology clinic were treated with cardiac medications; 39 (22.3%) were treated with ACE inhibitors, 22 (12.6%) were treated with beta-blockers, and 24 (13.7%) were treated with both. Multiple medications were prescribed for 90 (51.4%) patients.

Overall patient outcomes are described in Table 6. The majority (331, 77.3%) of patients were alive as of January 2013, and 93 (21.7%) patients were deceased. The majority of deaths were due to cancer progression (81, 87.1%), followed by cardiac etiologies (6, 6.4%) and other causes (6, 6.4%). Patient outcomes are unknown for 4 (0.9%) patients due to incomplete follow-up.

4. Discussion

The evolution of personalized medicine has led to an increasing interest in the development and testing of targeted therapies in oncology. While cancer professionals have been well versed in the identification and treatment of toxicities associated with chemotherapy, there is less understanding of the short- and long-term consequences associated with targeted agents. The United Kingdom National Cancer Research Institute (NCRI) has recently published trastuzumab cardiac toxicity monitoring guidelines based on data obtained from original clinical trials [12]. In this retrospective observational study, we report on the clinical outcomes of cancer patients treated with chemotherapy and/or targeted agents who were referred to our dedicated cardiac oncology clinic. While the majority of referrals to our clinic were breast cancer patients with decreased LVEF, 40% were patients with other tumour types (gastrointestinal, genitourinary, and hematologic) with a wide variety of cardiovascular issues including coronary artery disease, arrhythmias, and angina. The majority of patients were able to complete their prescribed cancer therapy (224, 60.4%), of which 191 (85.3%) did so during or after completing cardiac therapy. In cases where a change in therapy was not required, the cardiac oncology assessment often resulted in reassurance to both the patient and the referring physician. A total of 105 (30.8%) patients discontinued cancer treatment earlier than planned, mainly due to disease progression. These findings are consistent with an earlier review of our clinical data, specifically in the breast cancer population [11].

In this study, data was collected retrospectively from a variety of sources including hospital records (e-charts and paper charts) and nonhospital based imaging centers. We included all cancer patients referred to our clinic (including early and late stage disease), thus making conclusions about clinical outcomes difficult in such a heterogeneous population. We did not collect data on radiation therapy in our early patient database; future registries should also include this information. Our data would suggest that with appropriate cardiac management, many cancer patients could complete their prescribed therapy; however a case-cohort study would provide stronger evidence to support this statement.

Since the inception of our clinic, a number of similar cardiac oncology clinics have been introduced across North America. To our knowledge, this study is the first to describe a patient population specifically referred for cardiac oncology care and to characterize clinical outcomes. If we are to advance patient care and the growing field of cardiac oncology, it is imperative that we collaborate with our multidisciplinary colleagues. The National Cancer Institute (NCI) and National Heart, Lung and Blood Institute (NHLBI) recently sponsored a two-day workshop to identify the knowledge gaps in the field of cardiac oncology. Highlights of the workshop recommendations included the promotion of clinical research in the early identification and treatment of cardiotoxicity, as well as the need to identify the long-term cardiac consequences of these therapies in cancer survivors [13]. In conjunction with the Canadian Cardiac Oncology Network (CCON), we are in the process of formulating a national prospective clinical cardiac oncology registry, which will capture clinical data in real time, and allow sharing of data with other cardiac oncology clinics throughout Canada and eventually North America.

In summary, while cancer therapy continues to improve patient outcomes, the risk of unintended toxicities, such as cardiotoxicity, remains a concern. Our dedicated cardiac oncology clinic aims to identify patients at risk of cancer therapy-related cardiac complications, so that these issues can be managed and long-term sequelae avoided. From the perspective of the referring oncologist, a dedicated cardiac oncology clinic provides reassurance with management of high risk patients and streamlines communication between

specialties. Research efforts are underway to develop practical cardiac risk stratification tools, in order to select oncology patients who may benefit from more intensive cardiac monitoring during cancer therapy and follow-up. Through regular review of cardiac oncology clinic referral patterns, management plans, and patient outcomes, we aim to continuously improve the delivery of cardiac care to our patient population while optimizing cancer therapy and to conserve valuable resources by creating efficiencies within the health system.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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