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Left Ventricular Dysfunction in Patients Receiving Cardiotoxic Cancer Therapies

Are Clinicians Responding Optimally?

Geoffrey J. Yoon, MD,* Melinda L. Telli, MD,† David P. Kao, MD,‡ Kelly Y. Matsuda, PharmD,* Robert W. Carlson, MD,† Ronald M. Witteles, MD*

Stanford, California; and Denver, Colorado

Objectives The purpose of this study was to examine treatment practices for cancer therapy-associated decreased left ventricular ejection fraction (LVEF) detected on echocardiography and whether management was consistent with American College of Cardiology/American Heart Association guidelines.

Background Patients treated with anthracyclines or trastuzumab are at risk of cardiotoxicity. Decreased LVEF represents a Class I indication for drug intervention according to American College of Cardiology/American Heart Association guidelines.

Methods Patients receiving anthracycline or trastuzumab at Stanford University from October 2005 to October 2007 and who had undergone echocardiography before and after receiving an anthracycline or trastuzumab were identified. Chart review examined chemotherapy regimens, cardiac risk factors, imaging results, concomitant medications, and cardiology consultations.

Results Eighty-eight patients received therapy with an anthracycline or trastuzumab and had a pre-treatment and follow-up echocardiogram. Ninety-two percent were treated with anthracyclines, 17% with trastuzumab after an anthracycline, and 8% with trastuzumab without previous treatment with anthracycline. Mean baseline LVEF was 60%, with 14% having a baseline <55%. Forty percent had decreased LVEF (<55%) after anthracycline and/or trastuzumab treatment. Of these patients, 40% received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, 51% beta-blocker therapy, and 54% cardiology consultation. Of patients with asymptomatic decreased LVEF, 31% received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, 35% beta-blocker therapy, and 42% cardiology consultation. Of those with symptomatic decreased LVEF, 67% received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, 100% beta-blocker therapy, and 89% cardiology consultation.

Conclusions Many cancer survivors are not receiving treatment consistent with heart failure guidelines. There is substantial opportunity for collaboration between oncologists and cardiologists to improve the care of oncology patients receiving cardiotoxic therapy. (J Am Coll Cardiol 2010;56:1644–50) © 2010 by the American College of Cardiology Foundation

The understanding and treatment of heart failure and decreased left ventricular ejection fraction (LVEF) have undergone a radical change during the past 2 decades. It is now understood that institution of medical therapy can often prevent or reverse progressive left ventricular (LV) dysfunction and is ideally instituted before heart failure symptoms develop (1). Heart failure is generally thought to be a progressive clinical syndrome with symptoms of congestion occurring late in the natural history of the disease. As such, current treatment guidelines emphasize prevention and early intervention for at-risk individuals and individuals with asymptomatic decreased LVEF (1).

Asymptomatic decreased LVEF can lead to a markedly increased risk of the development of congestive heart failure and death (2). Asymptomatic decreased LVEF is a Class I indication for therapy with beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor

From the *Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California; †Division of Medical Oncology, Stanford University School of Medicine, Stanford, California; and the ‡Division of Cardiovascular Medicine, University of Colorado School of Medicine, Denver, Colorado. Dr. Matsuda has served as a consultant to Medicure Pharma. All other authors have reported that they have no relationships to disclose. This work was presented as an abstract at the 2009 American College of Cardiology 58th Annual Scientific Session, Orlando, Florida, March 29 to 31, 2009, at the 2009 American College of Cardiology Consumer Interest Press Conference, March 28, 2009, and at the 2009 Annual Meeting of the American Society of Clinical Oncology, Orlando, Florida, May 29 to June 2, 2009.

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blockers (ARBs) according to American College of Cardiology/American Heart Association guidelines (1,3).

Anthracyclines and trastuzumab are used to treat cancer and have known cardiotoxicity. Anthracyclines such as doxorubicin directly damage the myocardium through production of oxygen free radicals, leading to LV dysfunction and, in some cases, an irreversible cardiomyopathy (4). This toxicity is cumulative and dose dependent with an incidence of clinically detected heart failure in 2.2% of patients receiving doxorubicin at a median dose of 390 mg/m^2 (5). Importantly, these early studies focused only on patients in whom symptomatic heart failure developed.

Studies incorporating prospective LVEF monitoring demonstrate that asymptomatic cardiotoxicity is common, even at lower cumulative doses. The most commonly accepted definition of decreased LVEF in the oncology community is an absolute 10-point decrease in LVEF from baseline or an LVEF <50% (6). Prospective studies have observed doxorubicin-related decreased LVEF in 16%, 38%, and 65% of patients receiving doxorubicin cumulative doses of 300 mg/m^2, 450 mg/m^2, and 550 mg/m^2, respectively (7).

Trastuzumab (Herceptin, Genentech, South San Francisco, California) is a humanized monoclonal antibody against the extracellular domain of HER2 and is part of the standard treatment for breast cancer with HER2 overexpression and/or amplification. In the pivotal phase III clinical trial, a 27% incidence of cardiac dysfunction was observed in metastatic breast cancer patients treated with concurrent doxorubicin and trastuzumab, and 13% in patients treated with concurrent trastuzumab and paclitaxel, almost all of whom had received previous anthracycline therapy (8). Subsequent studies in patients with early-stage breast cancer demonstrated symptomatic heart failure in as many as 4% and asymptomatic decreased LVEF in as many as 14% of patients treated sequentially with anthracycline- and trastuzumab-containing regimens (9–14). Due to the known cardiotoxicity of trastuzumab, the package insert recommends baseline LVEF assessment and reassessment every 3 months during and upon completion of this therapy (15).

In clinical oncology practice, asymptomatic decreases in LVEF are the most commonly encountered form of cardiotoxicity (7,16). We designed this study to examine how clinicians have been treating cancer patients with decreased LVEF after exposure to anthracyclines and/or trastuzumab and specifically to examine whether the care provided after diagnosis of decreased LVEF is consistent with the American College of Cardiology/American Heart Association guidelines.

Methods

After institutional review board approval, we identified all patients who received anthracycline and/or trastuzumab cancer therapy at Stanford University from October 1, 2005, to October 31, 2007, using an institutional pharmacy database. A total of 974 patients received an anthracycline and/or trastuzumab during this time period. We identified all unique patients who had at least 1 echocardiogram (echo) performed before and after the start of chemotherapy using an institutional echocardiography database. All echos were 2-dimensional transthoracic echos, and all were interpreted by cardiologists at Stanford University.

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin receptor blocker
CI = confidence interval
echo = echocardiogram
LV = left ventricular
LVEF = left ventricular ejection fraction
MUGA = multiple gated acquisition
OR = odds ratio

During the time period of this study, some patients receiving an anthracycline and/or trastuzumab had cardiac monitoring with multiple gated acquisition (MUGA) scan. To compare patients who underwent MUGA imaging with patients who underwent echocardiographic imaging, we used a random number generator to choose 400 charts from the original chemotherapy database. Among this group, 88 patients were identified who had MUGA imaging performed before anthracycline and/or trastuzumab exposure and represented our comparison cohort.

Detailed chart review was then conducted examining demographic data including age, sex, cancer disease characteristics, cancer therapy type and dose, presence of pre-existing cardiac disease and cardiac risk factors, cardiac imaging indication and results, concomitant medications, and cardiology consultations. We also examined individual charts to determine whether a contraindication to beta-blocker or ACEI/ARB therapy existed. Patients in both inpatient and outpatient settings were evaluated in this study.

Patients were defined as having decreased LVEF if they had an LVEF <55%, according to our institutional standard. We defined symptomatic decreased LVEF as an LVEF <55% with the presence of dyspnea, orthopnea, pulmonary edema, lower extremity edema, and/or ascites that clinicians attributed to congestive heart failure. We recorded the background rate at Stanford Hospital and Clinics for the treatment of LV systolic dysfunction with ACEI/ARB therapy from Hospital Compare data (17).

Statistical analysis. Descriptive statistics were used to calculate the number of patients experiencing decreased LVEF, both with and without symptoms. For patients with an LVEF <55%, we calculated the proportion of patients who received: 1) ACEI/ARB therapy; 2) beta-blocker therapy; and 3) cardiology consultation. Odds ratios (ORs) and their 95% confidence intervals (CIs) were used to evaluate the relationship of cardiac risk factors to the development of decreased LVEF.

Results

Patient characteristics. A total of 88 patients met inclusion criteria. Their baseline characteristics before the start of treatment with cardiotoxic chemotherapy are listed in Table 1.

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Table 1 Baseline Characteristics of Patients (n = 88)

Mean age, yrs (range)	51.6 (23–78)
Sex, n (%)	
Male	41 (47)
Female	47 (53)
Baseline LVEF, % ± SD	60 ± 8
Patients with baseline LVEF below normal, n (%)	12 (14)
Cardiac risk factors, n (%)	
Coronary artery disease	6 (7)
Diabetes mellitus	15 (17)
Hypercholesterolemia	23 (26)
Hypertension	28 (32)
Taking ACEI/ARBs, n (%)	15 (17)
Taking beta-blockers, n (%)	16 (18)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction.

Presence of pre-existing coronary artery disease and cardiac risk factors of hypertension, diabetes, and hypercholesterolemia are listed in Table 1. Other pre-existing cardiac diseases were noted: 1 patient had pulmonary hypertension, 1 patient had a ventricular septal defect, 1 patient had a history of supraventricular tachycardia, and 1 patient had a history of orthotopic heart transplantation for ischemic cardiomyopathy. Seventeen patients were screened for cardiac ischemic disease before chemotherapy with stress equilibrium-gated nuclear angiocardiography, stress echocardiography, and/or cardiac catheterization, resulting in the diagnosis of coronary artery disease in 3 patients.

Patients in the study had a baseline LVEF of 60% (±8%). Fifteen patients (17%) were taking ACEI/ARBs and 16 patients (18%) were taking beta-blockers before chemotherapy.

The majority of patients had breast cancer (32%) or acute myelogenous leukemia (32%). A breakdown of the malignancies treated is included in Table 2. Table 3 lists chemotherapy regimens and cumulative doses. Most patients (92%) received anthracyclines. Seven patients (8%) received trastuzumab and had no exposure to an anthracycline. Fifteen patients (17%) received trastuzumab after exposure to an anthracycline.

Patients experiencing decreased LVEF. A total of 88 patients had echos before and after the start of cancer therapy. The mean follow-up from the start of cancer therapy to the last follow-up echo was 11.9 ± 11.7 months. Common indications for ordering echos after chemotherapy included post-chemotherapy surveillance, chest pain, fever, and suspected pericardial disease.

Table 2 Cancer Diagnosis (n = 88)

Breast cancer, n (%)	28 (32)
Acute myelogenous leukemia, n (%)	28 (32)
Chronic myelogenous leukemia, n (%)	2 (2)
Acute lymphoblastic leukemia, n (%)	9 (10)
Non-Hodgkin's lymphoma, n (%)	11 (13)
Hodgkin's lymphoma, n (%)	2 (2)
Other, n (%)	8 (9)

Table 3 Cancer Therapy and Cumulative Dose (n = 88)

Cancer Therapy	n (%)	Cumulative Dose (Mean ± SD)
All anthracyclines	81 (92)	N/A
Doxorubicin	49 (56)	238 ± 167 mg/m^2
Daunorubicin	17 (19)	216 ± 112 mg/m^2
Idarubicin	15 (17)	40 ± 9 mg/m^2
Trastuzumab with no exposure to anthracycline	7 (8)	210 ± 161 mg/kg
Trastuzumab after exposure to anthracycline	15 (17)	91 ± 73 mg/kg (trastuzumab)

N/A = not applicable.

A total of 35 patients had decreased LVEF after the start of chemotherapy. Twelve patients had a baseline LVEF below normal before chemotherapy and had a diagnosis of a low LVEF as outpatients. In 23 patients, a low LVEF developed after cancer therapy, and 22 of these patients (96%) had a diagnosis of a low LVEF as outpatients.

Of the 35 total patients who had a decreased LVEF after the start of chemotherapy, 14 (40%) received ACEI/ARB therapy, 18 (51%) received beta-blocker therapy, and 19 (54%) received cardiology consultation (Fig. 1). The background rate at Stanford Hospital and Clinics for the treatment of LV systolic dysfunction with ACEI/ARB therapy is 98% (17).

Nine patients in the study had symptomatic decreased LVEF after the start of chemotherapy. Six patients (67%) in this cohort received ACEI/ARB therapy, 9 (100%) received

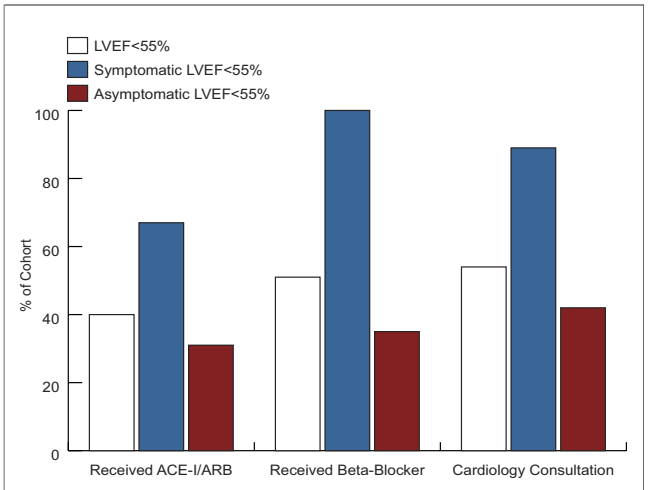

Figure 1 Percentage of Patients Who Received ACEIs/ARBs, Beta-Blockers, and/or Cardiology Consultation After the Start of Chemotherapy

Open bars on the bar graph represent the percentage of patients with left ventricular ejection fraction (LVEF) <55% who received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs), beta-blockers, and/or cardiology consultation. **Blue bars** represent the percentage of patients with a symptomatic LVEF <55%, and **red bars** represent the percentage of patients with an asymptomatic LVEF <55% who received ACEI/ARBs, beta-blockers, and/or cardiology consultation.

beta-blocker therapy, and 8 (89%) received cardiology consultation (Fig. 1). Of the 8 patients with symptomatic decreased LVEF who received cardiology consultation, 5 (63%) received ACEI/ARB therapy and 100% received beta-blocker therapy. The 1 patient with symptomatic decreased LVEF who did not receive cardiology consultation received ACEI/ARB and beta-blocker therapy.

Twenty-six patients in the study had asymptomatic decreased LVEF after the start of chemotherapy. Eight patients (31%) with asymptomatic decreased LVEF received ACEI/ARB therapy, 9 (35%) received beta-blocker therapy, and 11 (42%) received cardiology consultation (Fig. 1). Of the 11 patients with asymptomatic decreased LVEF who received cardiology consultation, 5 (45%) received ACEI/ARB therapy and 4 (36%) received beta-blocker therapy. Of the 15 patients with asymptomatic decreased LVEF who did not receive cardiology consultation, 3 (20%) received ACEI/ARB therapy and 4 (27%) received beta-blocker therapy.

Within the group of patients with asymptomatic or symptomatic decreased LVEF, there were no allergies to ACEI/ARB therapy or beta-blockers. For patients with decreased LVEF, physician assessment after diagnosis of decreased LVEF on echocardiography did not document any contraindications to receiving ACEI/ARB therapy or beta-blocker therapy. All 35 patients who had decreased LVEF had a creatinine clearance >30 ml/min at the start of their anthracycline or trastuzumab treatment, as determined by the Cockcroft-Gault formula (18).

Of the 21 patients who had decreased LVEF and did not receive ACEI/ARBs, 12 had anemia with a mean hemoglobin level of 10.6 ± 1.1 g/dl (range 9.2 to 11.9 g/dl) during physician assessment after a diagnosis of decreased LVEF. None of the 21 patients in this cohort had fatigue or hypotension (systolic blood pressure <100 mm Hg and/or diastolic blood pressure <60 mm Hg) during physician assessment after a diagnosis of decreased LVEF.

Of the 16 patients who had decreased LVEF and did not receive beta-blockers, 10 had anemia with a mean hemoglobin level of 10.5 ± 1.0 g/dl (range 9.3 to 11.9 g/dl) during physician assessment after a diagnosis of decreased LVEF. None of the 16 patients in this cohort had fatigue or hypotension (systolic blood pressure <100 mm Hg and/or diastolic blood pressure <60 mm Hg) during physician assessment after a diagnosis of decreased LVEF.

Potential risk factors for cardiotoxicity. Twenty-one patients had a baseline LVEF that was normal and a decreased LVEF developed after the start of anthracycline or trastuzumab therapy. Only hypercholesterolemia (OR: 3.76, 95% CI: 1.29 to 11.0; p = 0.014) was associated with the development of decreased LVEF after the start of chemotherapy, whereas age older than 65 years (OR: 1.06, 95% CI: 0.340 to 3.39; p = 0.920), male sex (OR: 2.57, 95% CI: 0.954 to 6.89; p = 0.062), coronary artery disease (OR: 1.59, 95% CI: 0.296 to 8.64; p = 0.624), hypertension (OR: 0.926, 95% CI: 0.330 to 2.62; p = 0.888), and diabetes mellitus (OR: 1.36, 95% CI: 0.419 to 4.46; p = 0.623) were not associated with the development of decreased LVEF, although our small sample size makes the power to detect clinically meaningful associations quite low.

Thirteen patients (15%) had left chest wall radiation therapy and 7 patients (8%) had mediastinal radiation therapy. Mediastinal and left chest wall radiation was not associated with the development of decreased LVEF (OR: 2.22, 95% CI: 0.464 to 10.677, p = 0.346 and OR: 0.444, 95% CI: 0.100 to 2.03; p = 0.316, respectively), although the numbers were small.

All 4 patients with other cardiac risk factors (pulmonary hypertension, supraventricular tachycardia, ventricular septal defect, and post-transplantation status) had a baseline LVEF >55%, and progressed to a decreased LVEF after the start of anthracycline or trastuzumab therapy.

Comparison between MUGA and echo groups. Tables 4 and 5 compare 88 patients who received MUGA imaging with the 88 study patients who received an echo before cancer therapy. There was no statistically significant difference in deaths between MUGA and echo groups during the study period, as shown in Table 5 (p = 0.71). There was also no difference in deaths in patients with an LVEF <55% between MUGA and echo groups (p = 0.21).

Patients who had MUGA imaging before cancer therapy and who had a low LVEF after cancer therapy actually had lower rates of receiving beta-blockers and cardiology consultation compared with the echo group, as shown in Table 5 (6% received beta-blockers vs. 51% in the echo group

Table 4 Baseline Characteristics of Patients Who Underwent MUGA Imaging Compared With Echocardiographic Imaging Before Cancer Therapy

	MUGA (n = 88)	Echo (n = 88)	p Value*
Mean age, yrs (range)	56.4 (29–89)	51.6 (23–78)	0.01
Sex, n (%)			
Male	18 (20)	41 (47)	<0.001
Female	70 (80)	47 (53)	<0.001
Baseline LVEF, % ± SD	65.8 ± 8.6	60 ± 8	<0.001
Patients with baseline LVEF below normal, n (%)	7 (8)	12 (14)	0.23
Cardiac risk factors, n (%)			
Coronary artery disease	1 (1)	6 (7)	0.054
Diabetes mellitus	10 (11)	15 (17)	0.28
Hypercholesterolemia	13 (15)	23 (26)	0.06
Hypertension	20 (23)	28 (32)	0.18
Taking ACEI/ARBs, n (%)	13 (15)	15 (17)	0.68
Taking beta-blockers, n (%)	7 (8)	16 (18)	0.04
Cancer diagnosis, n (%)			
Breast cancer	55 (63)	28 (32)	<0.001
Acute myelogenous leukemia	1 (1)	28 (32)	<0.001
Chronic myelogenous leukemia	0 (0)	2 (2)	0.16
Non-Hodgkin's lymphoma	18 (20)	11 (13)	0.16
Hodgkin's lymphoma	2 (2)	2 (2)	1.0
Other	12 (14)	8 (9)	0.34

*p value calculated using chi-square analysis.
echo = echocardiogram; MUGA = multiple gated acquisition; other abbreviations as in Table 1.

Table 5 Deaths and Cardiovascular Treatments of Patients Who Underwent MUGA Imaging Compared With Echocardiographic Imaging Before Cancer Therapy

	MUGA (n = 88)	Echo (n = 88)	p Value*
Deaths, n (%)	20 (23)	18 (20)	0.71
LVEF <55%, n (%)	16 (18)	35 (40)	0.002
Deaths within group LVEF <55%, n (%)	2 (13)	10 (29)	0.21
Cardiovascular treatments, n (%)			
Patients with LVEF <55% who received ACEI/ARB	4 (25)	14 (40)	0.30
Patients with LVEF <55% who received beta-blocker	1 (6)	18 (51)	0.002
Patients with LVEF <55% who received cardiology consultation	3 (19)	19 (54)	0.02

*p value calculated using chi-square analysis.
Abbreviations as in Tables 1 and 4.

[$p < 0.05$]; 19% received cardiology consultation vs. 54% in the echo group [$p < 0.05$]). There was no difference in those who received ACEI/ARB therapy between MUGA and echo groups for patients with a low LVEF (25% received ACEI/ARB vs. 40% in the echo group [$p = 0.30$]).

Patient deaths. Of the 35 patients with a low LVEF, 10 (29%) died during the study period. Four patients had a baseline LVEF <55% diagnosed as outpatients before cancer therapy. Of these 4 patients with a decreased baseline LVEF, 1 received ACEI/ARB therapy, 3 received beta-blocker therapy, and 1 received cardiology consultation. Decreased LVEF developed in 6 patients after cancer therapy, and diagnosed with outpatient echocardiograms. Of these 6 patients, 3 (50%) received ACEI/ARBs, 4 (67%) received beta-blockers, and 3 (50%) received cardiology consultation.

Of the original 88 patients in the study, 18 died during the study period. Eleven patients died of septic shock, 3 of malignancy, 2 of noncardiac respiratory failure, and 1 of intracranial hemorrhage. One patient died of ventricular tachycardia in the setting of severe hypokalemia due to antifungal therapy. There were no deaths from congestive heart failure. Of the patients who died, 9 had acute myelogenous leukemia, 5 had acute lymphoblastic leukemia, 1 had chronic myelogenous leukemia, 1 had non-Hodgkin's lymphoma, 1 had Hodgkin's lymphoma, and 1 had breast cancer.

Discussion

This is the first study to evaluate cardiovascular treatment and referral practices for cancer patients with treatment-related decreased LVEF. Our study demonstrates that many cancer patients with asymptomatic decreased LVEF are not receiving cardiovascular care consistent with guideline recommendations. Specifically, many patients with asymptomatic decreased LVEF are not receiving American College of Cardiology/American Heart Association Class I-indicated beta-blocker or ACEI/ARB therapy. Many patients with asymptomatic decreased LVEF are also not receiving cardiovascular specialty consultation. In contrast, the majority of patients who developed symptomatic decreased LVEF related to cardiotoxic cancer therapy received treatment with ACEI/ARB therapy, beta-blocker therapy, and cardiology consultation.

The reasons for the lack of treatment and referral of patients experiencing asymptomatic decreased LVEF were not evaluated in our study. Possible explanations include a lack of knowledge of these treatment guidelines by the clinicians who care for these patients or beliefs among physicians that these declines in cardiac function are transient and reversible. Patient-related factors may also be relevant as patients may focus on their cancer treatment primarily and neglect or de-emphasize other aspects of their general medical care.

Our data demonstrate that many in our cohort had cancer diagnoses with poor prognoses, and we observed a high rate of mortality during our study period; this may be yet another factor that influenced the decision not to institute cardiac-specific treatment in cases of asymptomatic decreased LVEF, particularly in patients with acute leukemia. Nonetheless, the majority of patients with decreased LVEF were diagnosed as outpatients. As noted earlier, further review of the cases did not yield any other contraindications such as hypotension, fatigue, and severe anemia to explain the lack of treatment. In addition, patients in our study in whom decreased LVEF developed and who died during the study period had higher rates of receiving ACEI/ARB and beta-blocker therapy compared with the entire cohort with an LVEF <55%, although the numbers were small. Given the complex nature of heart failure cases among patients with cancer, it may be advisable to involve heart failure specialists early after the diagnosis of a decreased LVEF because heart failure survival has been demonstrated to improve with specialty care (19).

Transient decreases in the LVEF can occur after exposure to anthracyclines or trastuzumab. The long-term significance of transient decreases in LVEF during cancer therapy is not well-known, although data suggest that the response to injury of various causes is similar, with negative remodeling leading to progressive LV dysfunction over time (1). Initial recovery of LV function does not imply that the injury was "reversible" and without future consequence. Early decreases in the LVEF after chemotherapy may be associated with significant cardiotoxicity at a later time (20). In this study, we do not know whether subsequent imaging beyond the study's follow-up period showed an improvement in the LVEF.

Currently, given a paucity of long-term follow-up data, there is no clear way to predict which patients will develop transient versus worsening declines in their LVEF after chemotherapy, and clinicians may find it challenging to decide whether to start ACEI/ARBs and beta-blocker therapy. In similar situations with myocardial injury, such as with an episode of myocardial infarction, myocarditis, and various nonischemic heart failure causes, transient decreases

in LVEF may occur and frequently normalize after intervention. These patients may be at increased risk of subsequent LV dysfunction and clinical heart failure, and it is on this basis that many of these patients, particularly after myocardial infarction, receive ACEI/ARB and beta-blocker therapy regardless of their LV function, as is clearly recommended in current heart failure treatment guidelines (1).

During the study period, there were no deaths from heart failure and no hospitalizations due to heart failure. The patients who died in this study died of a variety of causes, not including heart failure, and it is unclear whether treatment with ACEI/ARBs and beta-blockers is specifically valuable in this patient population.

As shown by the SOLVD (Studies of Left Ventricular Dysfunction) investigators (3), treatment of asymptomatic decreased LVEF of various causes with ACE inhibition has been shown to decrease the incidence of symptomatic heart failure and improve outcomes. However, it is not clear whether treatment of asymptomatic decreased LVEF in cancer patients specifically decreases the risk of symptomatic heart failure. There are no prospective studies evaluating whether the treatment of asymptomatic decreased LVEF reduces hospitalizations or improves longevity or quality of life in this population. Observational studies show a higher incidence of LVEF recovery in cancer patients with a decreased LVEF treated with ACEI/ARBs (21,22). These data suggest that cancer patients who experience a decreased LVEF may have a response similar to that in patients in the general population with decreased LVEF who receive Class I-indicated therapy.

Study limitations. Our study was limited by the retrospective nature of the available data. Although it is possible that we may have missed cardiology consultations and medical therapies received outside our institution, we extensively reviewed the chart for any updated medications and referrals before, during, and after cancer therapy.

Many patients who received cardiotoxic cancer therapy at our institution during the study period were excluded from the study based on the lack of echos before and after the start of chemotherapy. Although there are professional society recommendations for pre- and post-chemotherapy echocardiographic screening, such as suggested by the American Society of Echocardiography (23), these recommendations are not uniform, particularly among oncology societies. Many patients who received cardiotoxic cancer therapy at our institution may not have had an assessment of LV function after cancer therapy because there are no clear guidelines for post-cancer therapy screening. Many patients excluded from the study may have had cardiac monitoring performed using MUGA scans. This study focused on clinicians' responses to decreased LVEF found during cardiac screening by echocardiography rather than on the rates of screening studies performed. In addition, the choice of using MUGA versus echocardiography for assessment of LV function is predominantly practitioner-dependent at our institution. Regardless of which imaging modality determined a decrease in LVEF, guideline-based therapy would recommend treatment with beta-blockers and ACEI/ARBs unless an appropriate contraindication was present.

Our study is also limited by the relatively small sample size, which limits the statistical power to detect clinically meaningful associations with risk factors, specific agents, and diseases. Previous studies have observed advanced age, hypertension, diabetes mellitus, coronary artery disease, and radiation as risk factors for the development of decreased LVEF from chemotherapy (7,24–26). Our study found that only hypercholesterolemia was associated with the development of decreased LVEF in patients who had normal LVEFs before chemotherapy. Due to the lack of statistical power for these subjects, these results should be interpreted with caution. There is potential for further investigation regarding the relationship between hypercholesterolemia and cardiotoxicity, as studies in mice have shown that pretreatment with statins may help to prevent anthracycline-induced cardiotoxicity (27).

Conclusions

We report here the first evaluation of cardiovascular treatment and consultation practices for cancer patients experiencing decreased LVEF outside the confines of a prospective clinical trial. The vast majority of patients in our study with symptomatic decreased LVEF received cardiology consultation and ACEI/ARB therapy, and all received beta-blocker therapy. However, the majority of cancer patients in our study with asymptomatic decreased LVEF did not receive ACEI/ARB or beta-blocker therapy according to American College of Cardiology/American Heart Association guidelines. This suggests that closer collaboration between cardiologists and oncologists is needed and may have implications for the prevention and treatment of cardiovascular toxicity among cancer survivors.

Reprint requests and correspondence: Dr. Ronald M. Witteles, Division of Cardiovascular Medicine, Stanford University School of Medicine, Falk CVRC 273, 300 Pasteur Drive, Stanford, California 94305-5406. E-mail: witteles@stanford.edu.

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