The Use of Cardiac Resynchronization Therapy in Cancer Patients with Heart Failure

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Abstract

Objectives: Investigate the use of cardiac resynchronization therapy (CRT) in cancer patients with heart failure (HF); assess factors associated with ischemic and non-ischemic HF.

Background: Many newer cancer therapies are cardiotoxic; thus, the incidence of HF has been increasing in this high-risk patient population. CRT has beneficial effects on morbidity, mortality, and left ventricular function in patients with non-ischemic cardiomyopathy, yet cancer patients and survivors who develop severe HF and are eligible for CRT often does not receive it.

Methods: Review of 2 years of echocardiography and electrocardiography data from cancer patients.

Results: Of 272 patients meeting inclusion criteria for CRT placement (LVEF ≤35%, QRS duration ≥120 ms), 131 (48.2%) had HF with ischemic etiology and 141 (51.8%) had HF with non-ischemic etiology. Most patients had solid tumors, including breast, lung, sarcoma, and lymphoma (73.2%, n=199). Only 21.3% (58/272; 27 ischemic; 31 non-ischemic) underwent CRT placement, who were mostly women and those with solid tumors. Non-ischemic HF was significantly associated with younger age (<65 years) (OR=0.91; 95% CI=0.87–0.95) and female sex (OR=2.5; 95% CI=1.1–6.0). As expected, ischemic HF was significantly associated with history of myocardial infarction, diabetes, and cardiovascular disease.

Conclusion: CRT is underutilized in cancer patients with HF. Most of the cancer patients who did not receive CRT had non-ischemic HF secondary to chemotherapy. CRT may be less utilized in those patients due to shortened life expectancy, yet evidence suggests that CRT has beneficial effects on morbidity, mortality, and left ventricular function. Its use may improve patient quality of life and allow oncologists to continue cancer treatments that could prolong survival.

Condensed Abstract

The advent of new cancer therapies has led to an increase in the number of long-term cancer survivors. However, many of these therapies are cardiotoxic, and thus the incidence of heart failure (HF) has been increasing in this high-risk patient population. Despite the known benefits of cardiac resynchronization therapy (CRT), a substantial number of cancer patients and survivors who develop severe HF fail to receive indicated therapies such as CRT, even when they meet eligibility criteria. Optimization of recommended therapies such as CRT may improve patient quality of life and allow oncologists to continue cancer treatments that could prolong survival.

Keywords: Cancer; Heart Failure; Cardiac Resynchronization Therapy; Non-Ischemic Etiology; Chemotherapy-Induced Cardiomyopathy; Left Ventricular Ejection Fraction; Myocardial Infarction; Coronary Artery Disease; Diabetes Mellitus; Dyslipidemia

List of Abbreviations: ACEI: Angiotensin Converting Enzyme Inhibitor; CI: Confidence Interval; CRT: Cardiac Resynchronization Therapy; HF: Heart Failure; LVEF: Left Ventricular Ejection Fraction; OR: Odds Ratio; SD: Standard Deviation

Introduction

The advent of new cancer therapies has brought about an increase in the number of long-term cancer survivors. However, many of these newer therapies are cardiotoxic, and thus the incidence of heart failure (HF) has been increasing in this high-risk patient population. Cardiac resynchronization therapy (CRT) is one of the most significant advances in the treatment of patients experiencing severe HF with impaired ejection fraction and ventricular conduction disturbances [1-2]. The biventricular pacing induced by CRT has been shown to restore left ventricular synchrony, resulting in improved health outcomes [1,3-5].

Despite the known benefits of CRT for patients who meet criteria for placement, information about the use of this technology in cancer patients and cancer survivors with severe HF is limited. Because the ultimate goal in treating patients with cancer is to cure the disease, the adverse cardiac effects of treatment are often overlooked. For cancer survivors, ongoing care focuses mostly on intermediate and long-term monitoring for cancer recurrence, rather than on long-term monitoring for adverse effects from cancer treatment, such as cardiomyopathy and HF. As a consequence, a substantial number of cancer patients and survivors who develop severe HF fail to receive indicated therapies such as CRT, even when they meet eligibility criteria.

Heart Failure Etiology

HF may be of ischemic or non-ischemic etiology. In HF with ischemic etiology, ventricular dysfunction is a consequence of myocardial ischemia and infarction related to coronary atherosclerosis, manifested by a significant narrowing or occlusion of the coronary arteries noted on cardiac catheterization. Conversely, in non-ischemic cardiomyopathy, the weakened heart muscle can result from toxic injury (chemotherapeutic agents), infection, immunological abnormalities, or genetic factors. A significant proportion of patients with non-ischemic cardiomyopathy have idiopathic dilated cardiomyopathy, the cause of which has not been established and which is likely to be multifactorial, potentially including occult viral myocarditis, abnormalities of the immune system, infiltrative myocardial disease, or genetic factors. Oftentimes, determining non-ischemic cardiomyopathy as the exact etiology is made difficult by heterogeneity in definitions and diagnostic criteria. Many epidemiological and clinical studies simply classify patients as having non-ischemic cardiomyopathy if heart failure is present and there is no clinical or electrocardiographic evidence of coronary disease. In the cancer population, chemotherapy-induced cardiomyopathy is usually of non-ischemic etiology. A sub-analysis from a randomized clinical trial of patients with HF suggests that CRT has greater beneficial effects on morbidity, mortality, and left ventricular function in patients with non-ischemic cardiomyopathy [6]. Nonetheless, clinical guidelines for CRT use in the management of these patients are lacking.

Antineoplastic Agents and Heart Failure

A wide variety of antineoplastic agents can cause unintended consequences on to the cardiovascular system, leading to heart failure [7-11]. Given the high prevalence of cardiovascular disease and associated risk factors in the general population, patients may already have compromised cardiac function at the time of cancer diagnosis and before starting chemotherapy [12,13]. Furthermore, multiple risk factors such as hypertension, obesity, dyslipidemia, and metabolic syndrome can compromise the cardiovascular reserve and increase the likelihood of subsequent cardio-toxicity leading to HF [14].

Anthracyclines are the most frequently cited and well-studied class of cardiotoxic anticancer agents, and their use is limited by cumulative, dose-dependent toxicity [15-16]. Retrospective analyses from clinical trials in adults suggest that the incidence of HF due to doxorubicin was 1.7% at a cumulative dose of 300 mg/m^2, 4.7% at 400 mg/m^2, 15.7% at 500 mg/m^2, and 48% at 650 mg/m^2 [15].

Trastuzumab, a humanized anti-ErbB2 monoclonal antibody used in the treatment of breast cancer and metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric cancer, also is known for increased risk of cardio-toxicity, particularly when used with concomitant or sequential anthracyclines chemotherapy [17-21]. In one of the first clinical trials using trastuzumab for metastatic breast cancer, cardiotoxicity was noted in 27% of patients receiving trastuzumab concurrently with anthracyclines therapy and in 13% of patients receiving paclitaxel and trastuzumab [17]. Other agents that may cause heart failure in cancer patients include traditional chemotherapeutic agents such as cyclophosphamide, and docetaxel; and angio-genesis inhibitors, including bevacizumab and sunitinib [22-24].

In this study, we investigated CRT use in cancer patients with HF at our institution, a tertiary cancer center. We also assessed factors associated with the HF etiology, either ischemic or non-ischemic. The findings from this study have immense clinical significance. Optimization of recommended therapies such as CRT may improve patient quality of life and allow oncologists to continue cancer treatments that could prolong survival.

Methods

In this retrospective study, we reviewed echocardiography and electrocardiography data from patients with cancer who were seen in the Department of Cardiology at The University of Texas MD Anderson Cancer Center in Houston, Texas. Eligibility criteria were:
1)An echocardiogram performed between July 1, 2010, and June 30, 2012
2)A left ventricular ejection fraction (LVEF) of ≤35%, as measured by the biplane method of disks (modified Simpson's).
3)QRS duration of >120 ms.

The MD Anderson Institutional Review Board approved the study. A waiver of informed consent was granted, given the retrospective design of the study. Materials described in the manuscript, including de-identified raw data, are stored in a password-protected database in the MD Anderson Department of Nursing. Materials can be made available for noncommercial purposes without breaching participant confidentiality.

Prior to data collection, to ensure data quality and consistency, the primary investigator (APF) provided orientation and extensive training to the data abstractors. The data abstractors remained blind to the study questions to minimize review bias. To validate the proficiency of the data abstractors, a pilot data collection from 10% (n=27) of the sample patient records was collected separately by the principal investigator and data abstractors and compared for consistency. Variables for which there was more than a 2% discrepancy between data abstractors were reassessed, and all data discrepancies were resolved jointly by the principal investigator and the data abstractor.

Study Variables

Sociodemographic data extracted were age, sex, and ethnicity. Electronic medical charts were reviewed for HF etiology (ischemic or non-ischemic), cardiac risk factors (hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, myocardial infarction, family history of heart disease, and alcohol and tobacco use), LVEF, QRS duration, and cardiac medications (angiotensin converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [patients who were intolerant to ACEIs], and beta-blockers). The etiology of left ventricular dysfunction was verified with a myocardial perfusion stress test or a left heart catheterization and confirmed as either ischemic or non-ischemic. For purposes of this study, the diagnostic etiology of non-ischemic cardiomyopathy was established by a negative myocardial perfusion stress test or left heart catheterization.

Data Analyses

Descriptive statistics were utilized to describe the study population. To examine the prevalence of type of HF (ischemic/non-ischemic) in this study population, proportions and 95% binomial exact confidence limits for each type were calculated. Clinical and demographic characteristics were compared by type of HF, using the Wilcoxon rank-sum test, chi-squared test, or Fisher's exact test, depending on the distribution of the data. Univariate and multivariate logistic regression analyses were used to estimate the strength of association with HF etiology for the variables. Factors found to be significant ($p<0.20$) in the univariate analysis were included in the multivariate model; a p value of 0.20 was used as the cutoff because a more traditional value ($p<0.05$) often does not identify variables known to be important. Further variable selection in the multivariate model was conducted using backward elimination. To obtain the most parsimonious model, only variables with p values <0.05 were included in the final model. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL). All of the statistical tests were two-sided.

Results

Patient Characteristics

Of the 24,879 cancer patients with echocardiographic studies performed during the specified time period, 272 patients met inclusion criteria for CRT placement (LVEF ≤35% and QRS >120 ms). Of these patients, 58 (21.3%) had CRT implantation, and of those, 27 (46.6%) had ischemic etiology and 31 (53.4%) had non-ischemic etiology.

The mean age of the subjects was 67.1 years (range 23–92 years); most were white (71.0%) and male (65.1%). Most had solid tumors (73.2%, n=199), including breast, lung, sarcomas, and lymphoma; 70 (25.7%) had liquid tumors, such as leukemia. Anti-cancer therapies with known cardiotoxicity used in the treatment of these patients included doxorubicin in 25 patients (9.2%), trastuzumab in 7 patients (2.6%), combination therapy (chemotherapy and radiation) in 44 patients (16.2%), and mediastinal radiation in 41 patients (15.1%).

In addition to cancer and HF, patients in this study had multiple comorbid conditions, including hypertension (73.5%, n=200), dyslipidemia (61.8%, n=168), coronary artery disease (54.8%, n=149), and diabetes mellitus (37.9%, n=103). Patients taking HF medications included 90.8% (n=247) on beta-blockers, 50.0% (n=136) on ACEIs, and 14.3% (n=39) on angiotensin receptor blockers.

Ischemic versus Non-Ischemic Heart Failure

Table 1 compares the sociodemographic and clinical characteristics of patients with ischemic versus non-ischemic HF. Of the 272 patients, 131 (48.2%) had HF with ischemic etiology and 141 (51.8%) had HF with non-ischemic etiology. Patients with ischemic HF were mostly male (77.9% vs. 53.2%; $p<0.001$) and were more likely to have had a history of coronary artery disease ($p<0.001$), diabetes mellitus ($p=0.001$), dyslipidemia ($p<0.001$), myocardial infarction ($p<0.001$), or tobacco use ($p=0.002$). Patients with non-ischemic HF were younger (mean = 63.3 vs. 71.1 years; $p<0.001$) than those who had ischemic HF. Patients with ischemic HF were more likely to have been given beta-blockers (96.9% vs. 85.1% of patients with non-ischemic HF; $p=0.001$).

Characteristic	Type of Heart Failure		
	Ischemic (n = 131) N %	Non-Ischemic (n = 141) N %	p-value
Age (years)			<0.001*
Mean (SD)	71.1 (8.4)	63.3 (12.5)	

Characteristic	Type of Heart Failure				p-value
	Ischemic (n = 131)		Non-Ischemic (n = 141)		
	N	%	N	%	
<65	25	19.1	69	48.9	
≥65	106	80.9	72	51.1	
Sex					<0.001*
Female	29	22.1	66	46.8	
Male	102	77.9	75	53.2	
Ethnicity					0.008*
African-American	7	5.3	24	17.0	
Asian	0	0.0	1	0.7	
White	104	79.4	89	63.1	
Hispanic	14	10.7	20	14.2	
Other	6	4.6	7	5.0	
History of coronary artery disease					<0.001*
No	10	7.6	113	80.1	
Yes	121	92.4	28	19.9	
History of hypertension					0.091
No	28	21.4	44	31.2	
Yes	103	78.6	97	68.8	
History of diabetes mellitus					0.001*
No	67	51.1	102	72.3	
Yes	64	48.9	39	27.7	
History of dyslipidemia					<0.001*
No	31	23.7	73	51.8	
Yes	100	76.3	68	48.2	
Family history of heart disease					0.684
No	80	61.1	90	63.8	
Yes	51	38.9	51	36.2	
History of myocardial infarction					<0.001*
No	64	48.9	139	98.6	
Yes	67	51.1	2	1.4	
History of alcohol use					0.970
No	81	61.8	88	62.4	
Yes	50	38.2	53	37.6	
History of tobacco use					0.002*
No	51	38.9	81	57.4	
Yes	80	61.1	60	42.6	
ACE inhibitor					0.039*
No	57	43.5	79	56	
Yes	74	56.5	62	44	
Beta blocker					0.001*
No	4	3.1	21	14.9	
Yes	127	96.9	120	85.1	
Angiotensin receptor blocker					0.537
No	114	87	119	84.4	

Characteristic	Type of Heart Failure				p-value
	Ischemic (n = 131)		Non-Ischemic (n = 141)		
	N	%	N	%	
Yes	17	13	22	15.6	
CRT implantation (N=58)	27	46.6	31	53.4	0.782
Cancer Diagnosis					0.059
Liquid tumor (leukemia)	28	21.4	42	29.8	
Solid tumor (breast, lung, sarcoma, lymphoma)	100	76.3	99	70.2	
No Cancer	3	2.3	0	0.0	

*Significant at p<0.05.
Abbreviations: CRT, cardiac resynchronization therapy; SD, standard deviation.
Table 1: Sociodemographic and Clinical Characteristics of the Study Population (N=272)

Multivariate logistic regression analyses in Table 2 showed that non-ischemic HF was significantly associated with younger age (<65 years) (OR=0.91; 95% CI=0.87–0.95) and female sex (OR=2.5; 95% CI=1.1–6.0). As expected ischemic HF was significantly associated with a history of myocardial infarction, diabetes and coronary artery disease (p<0.001).

Variable		OR	95% CL upper bound	95% CL lower bound	p-value
Age	≥65	1.0		0.952	<0.001*
	<65	0.908	0.867		
Sex	Male	1.0		5.968	0.035*
	Female	2.523	1.067		
Myocardial infarction	No	1.0		0.123	<0.001*
	Yes	0.023	0.004		
Coronary artery disease	No	1.0		0.124	<0.001*
	Yes	0.052	0.022		
Diabetes mellitus	No	1.0		0.908	0.029*
	Yes	0.391	0.169		

*Significant at p<0.05.
Abbreviations: CI, confidence limit; OR, odds ratio.
Table 2: Multivariate Model of Chemo-induced Cardiomyopathy (Non-Ischemic HF)

There were no significant differences between the two groups with regard to cardiac risk factors for hypertension (p=0.091), family history of heart disease (p=0.684), or the use of alcohol (p=0.970).

CRT Placement versus no CRT Placement

The characteristics of patients who received CRT placement versus those who did not receive CRT are listed in Table 3. There were no significant differences between the two groups except for the patient's sex (p=0.036) and cancer diagnosis (p=0.037). Patients who received CRT implantation were mostly male (53.4% vs. 46.6%, p= 0.036) and had a solid tumor (lung, breast, sarcoma, lymphoma) versus a liquid tumor (leukemia) (86.2% vs 13.8%, p=0.037).

Characteristic	CRT (No) n = 214		CRT (Yes) n = 58		p-value
	N	%	N	%	
Age (years)					0.766
< 65	73	34.1	21	36.2	
≥65	141	65.9	37	63.8	
Sex					0.036*
Female	68	31.8	27	46.6	
Male	146	68.2	31	53.4	
Ethnicity					0.114
African-American	21	9.8	10	17.2	
Asian	1	0.5	0	0.0	
Caucasian	157	73.4	36	62.1	

Characteristic	CRT (No) n = 214		CRT (Yes) n = 58		
	N	%	N	%	p-value
Hispanic	23	10.7	11	19.0	
Other	12	5.6	1	1.7	
History of coronary artery disease					0.156
No	92	43.0	31	53.4	
Yes	122	57.0	27	46.6	
History of hypertension					0.374
No	54	25.2	18	31.0	
Yes	160	74.8	40	69.0	
History of diabetes mellitus					0.218
No	137	64.0	32	55.2	
Yes	77	36.0	26	44.8	
Family history of heart disease					0.320
No	137	64.0	33	56.9	
Yes	77	36.0	25	43.1	
History of dyslipidemia					0.720
No	83	38.8	21	36.2	
Yes	131	61.2	37	63.8	
History of myocardial infarction					0.922
No	160	74.8	43	74.1	
Yes	54	25.2	15	25.9	
History of alcohol use					0.769
No	132	61.7	37	63.8	
Yes	82	38.3	21	36.2	
History of tobacco use					0.351
No	107	50.0	25	43.1	
Yes	107	50.0	33	56.9	
Angiotensin converting enzyme inhibitor (ACEI)					1.000
No	107	50.0	29	50.0	
Yes	107	50.0	29	50.0	
Beta-blocker					0.310
No	22	10.3	3	5.2	
Yes	192	89.7	55	94.8	
Angiotensin receptor blocker					0.477
No	185	86.4	48	82.8	
Yes	29	13.6	10	17.2	
Cancer diagnosis					0.037*
Liquid tumor (leukemia)	62	29.0	8	13.8	
Solid tumor (breast, lung, sarcoma, lymphoma)	149	69.6	50	86.2	
No cancer	3	1.4	0	0.0	

* Significant at $p<0.05$.
Abbreviation: CRT, cardiac resynchronization therapy.
Table 3: Characteristics of Patients With and Without CRT Placement

Discussion

In 2001, CRT was approved by the US Food and Drug Administration for use in selected patients with left ventricular dysfunction. This included patients with moderate to severe HF (New York Heart Association functional class III to IV), with an LVEF of ≤35%, and QRS duration ≥120 ms despite optimal pharmacotherapy. The use of CRT was associated with survival benefit, left ventricular reverse remodeling, and reduced hospitalizations for patients with HF [25-27]. The primary finding in this study is that only a limited number of eligible cancer patients with HF received the device. To our knowledge, this is the first study to report on CRT utilization in cancer patients with HF.

HF in the general population typically is secondary to myocardial infarction, coronary artery disease, or hypertension [28]. Our results indicated that the patients with cancer in our sample were similar to patients in the general HF population, in terms of demographic characteristics and comorbidities (specifically, hypertension, hyperlipidemia, and coronary artery disease). It is imperative that cardiac risk factors be managed aggressively in patients with cancer to prevent development of HF. Moreover, patients in this cohort were on optimum HF medications including beta-blockers (90.8%) and ACEIs (50.0%) which are known to promote reverse ventricular remodelling and improvement in ejection fraction [29-31]. Clinical practice guidelines recommend CRT for appropriate patients who remain symptomatic despite optimal pharmacological therapy [28,32-34].

However, 10 (7.6%) patients with ischemic HF in this cohort had no known history of coronary artery disease. This can be explained by the fact that in patients with cancer, there are concomitant disease conditions that can result in ischemic cardiomyopathy in the absence of coronary artery disease. Ischemic cardiomyopathy can occur in embolic conditions (e.g., atrial fibrillation, endocarditis, thrombophilic states) and microvascular ischemia resulting from infiltrative myocardial disease (e.g., cardiac amyloidosis, hemochromatosis, and sarcoidosis), which are commonly seen in patients with cancer [35-39].

Cardiac amyloidosis is caused by tissue deposition of misfolded proteins that results in progressive organ damage [39]. The deposition is most common in the myocardium, causing the myocardium to become thick with a rubbery consistency [39]. High-grade infiltration (>50%) of the myocardium is most common in the immunoglobulin light-chain amyloidosis variety, and 90% of cases have microvascular involvement, resulting in tissue ischemia and infarction [38,40]. Resultant myocardial fibrosis adds to the myocardial dysfunction, causing heart failure and cardiac arrhythmias.

Although the specific etiology of left ventricular dysfunction leading to HF in this patient cohort was difficult to ascertain, we found that 51.8 % had HF with non-ischemic etiology. Non-ischemic HF can be caused by cancer therapies, infection, valvular disease, excessive alcohol use, and myocarditis. Indeed, in our multivariate model, we found that younger age and female sex were significantly associated with non-ischemic HF and that ischemic HF was significantly associated with a history of myocardial infarction, diabetes, and cardiovascular disease. Regardless of etiology, these patients were on optimum medical therapy as recommended by clinical guidelines; 90.8% (n=247) were taking beta-blockers, which are believed to have a cardio-protective benefit as a consequence of their potent antioxidant effects, modulation of neurohumoral factors, and modulation of cardiac electrophysiological properties [41]. This is significant because, despite receiving appropriate pharmacotherapy, all of the patients in our sample were eligible for CRT on the basis of LVEF and QRS parameters, yet more than three quarters of them had not received it at the time of their participation in the study. Adding CRT to optimal pharmacotherapy could be an effective approach for managing HF in patients with cancer and warrants further exploration in this growing patient population.

We reviewed data from July 01, 2010 to June 30, 2012. In 2012, the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society guidelines expanded the CRT indication to include patients with milder symptoms, for example, LVEF ≤30%, left bundle-branch block pattern, and QRS duration of >150 ms [26,42]. However, our inclusion criteria were based on the earlier guidelines that were available when we conducted the study. Consequently, with the expanded guidelines, even more cancer patients may be eligible for CRT than we observed in this study.

Limitations

There are limitations to this study. First, this is a retrospective study of a small patient sample in a tertiary cancer center and not fully representative of cancer patients with HF in general hospitals and community cancer centers. Data were abstracted from patient medical records by more than one person, which could have affected the accuracy, consistency, or completeness of the information extracted. It is possible that patients who appeared to be eligible for CRT in this study according to cancer diagnosis or treatment may have had other contraindications that were not reviewed. Nonetheless, we specifically manage patients with cancer in our cardiac practice; other practices with different patient populations or care patterns may not encounter this issue. In addition, because this is a cross-sectional study, the lack of follow-up data precludes assessment of benefit of CRT in improving health outcomes and whether a CRT device was subsequently implanted in eligible patients.

Conclusions

CRT is underutilized in cancer patients with HF. The findings from this study may provide preliminary information to assist in the development of a protocol that will identify cancer patients who may benefit from CRT implantation. Chemotherapy-induced cardiomyopathy, a most common cause of non-ischemic heart failure, will be an increasing clinical issue in cancer patients. When

HF has a non-ischemic etiology secondary to chemotherapy, CRT may be less utilized due to shortened life expectancy, yet some evidence suggests that CRT has beneficial effects on morbidity, mortality, and left ventricular function in patients with non-ischemic cardiomyopathy. Future prospective studies with larger sample sizes are needed.

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