Sub-acute Verses Late-onset Presentation of Oncotherapy Related Cardiotoxicity: Predictors of Cardiac Function Recovery and Long-Term Outcome

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ABSTRACT: **Background:** Cardiac damage caused by oncological therapy may manifest early or many years after the exposure.

Objectives: To determine the differences between sub-acute and late-onset cardiotoxicity in left ventricular ejection fraction (LVEF) recovery as well as long-term prognosis.

Methods: We studied 91 patients diagnosed with impaired systolic function and previous exposure to oncological therapy. The study population was divided according to sub-acute (from 2 weeks to ≤ 1 year) and late-onset (› 1 year) presentation cardiotoxicity. Recovery of LVEF of at least 50% was defined as the primary end point and total mortality was the secondary end point.

Results: Fifty-three (58%) patients were classified as sub-acute, while 38 (42%) were defined as late-onset cardiotoxicity. Baseline clinical characteristics were similar in the two groups. The mean LVEF at presentation was significantly lower among patients in the late-onset vs. sub-acute group (28% vs. 37%, respectively, P ‹ 0.001). Independent predictors of LVEF recovery were trastuzumab therapy and a higher baseline LVEF. Although long-term mortality rates were similar in the groups with sub-acute and late-onset cardiotoxicity, improvement of LVEF was independently associated with reduced mortality.

Conclusions: Our findings suggest that early detection and treatment of oncological cardiotoxicity play an important role in LVEF recovery and long-term prognosis.

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KEY WORDS: cardiotoxicity, left ventricular ejection fraction (LVEF), trastuzumab

The past four decades have witnessed a tremendous development in chemotherapeutic and other oncological therapies targeting a diverse group of malignancies. These agents have significantly improved survival rates in cancer patients, but at a cost of considerable adverse effects, including cardiotoxicity [1-3]. The incidence of cardiotoxicity varies considerably by the chemotherapeutic agents used [4,5].

The incidence of anthracycline cardiotoxicity varies greatly by the dose and the definition used, with estimated rates varying from 5% to 50%. This toxicity has been recognized to be cumulative and dose dependent [6,7]. Monoclonal antibodies such as trastuzumab have a considerable incidence of cardiotoxicity, although with less dose dependency [8,9]. Distinct types of presentation have been recognized according to the time of onset. Acute toxicity occurs after a single dose, or after a course of anthracyclines, with the onset of manifestations within 2 weeks after treatment. Sub-acute presentation is defined by diagnosis from 2 weeks to 1 year after the end of treatment. The late-onset/chronic form presents years or even decades later. The sub-acute and late-onset forms are the most commonly encountered and clinically relevant forms of cardiotoxicity in the outpatient situation.

Limited data exist regarding the outcomes of patients who develop chemotherapy-induced left ventricular dysfunction. Moreover, the differences in the clinical presentation and the outcome of patients with sub-acute vs. late-onset cardiotoxicity are poorly defined. Accordingly, the aim of the present study was to characterize a cohort of consecutive cardio-oncological patients with impaired systolic function and to define the predictors of LVEF recovery and long-term prognosis based on the mode of onset of cardiotoxicity.

PATIENTS AND METHODS

STUDY POPULATION

We conducted an observational study in the Heart Failure Institute at the Leviev Heart Center, Sheba Medical Center. The study was approved by the institutional review board. Sheba Medical Center is a tertiary care hospital, which includes Israel's leading cancer and hematology centers and treats approximately 4500 new cancer patients each year. Consecutive patients, older than 18 years of age who were referred to our clinic during years 1998–2016 with left ventricular systolic dysfunction (LVEF ≤ 45%) and a history of ongoing or past oncology therapy, were included in this study. Documentation of normal cardiac function by any imaging modality prior to initiation of cancer therapy was required. We did not include patients with acute anthracycline cardiotoxicity (n=3) since these patients were treated as an emergency situation. Patients with an alternative explanation for reduced LVEF (such

as significant coronary artery disease) were excluded. The date of the onset of cardiotoxicity was defined by the first abnormal echocardiogram demonstrating reduced LVEF. The study population meeting these inclusion criteria was 91 patients.

DATA RECORDING AND FOLLOW-UP

Medical records were examined for the oncological therapy received with particular attention focused on agents known to be associated with a risk of left ventricular dysfunction, such as adriamycin, trastuzumab, and other chest irradiations. Clinical data were collected on the type of malignancy, co-morbidities, New York Heart Association (NYHA) functional classification, and heart failure symptoms.

Echo-Doppler parameters include left atrial diameter (LAD), left ventricular dimensions, ejection fraction, estimated systolic pulmonary artery pressure (PAP), diastolic function, and the presence of valvular dysfunction. Significant valvular disease was considered to be of at least moderate severity. We defined significant diastolic dysfunction as pseudo-normal or restrictive left ventricular filling pattern.

Patients were treated and followed according to the contemporary heart failure guidelines. We hereby report a follow-up from the date of diagnosis of left ventricular dysfunction until the end of year 2016. Mortality data were obtained from the National Population Registry of Israel by matching patient identification numbers with their vital status.

DATA ANALYSIS

Left ventricular systolic function recovery was our primary end-point: demonstrating LVEF ≥ 50% on any follow-up echocardiogram. Mortality or heart transplantation was defined as the secondary endpoint.

Categorical variables are expressed as number and percent, and continuous variables are shown as mean ± SD. Comparisons of patients with sub-acute onset and chronic onset cardiotoxicity with left ventricular systolic dysfunction were conducted with chi-square and Fisher's exact test as appropriate for categorical variables and by paired Student's *t*-test for continuous variables. The same tests were used to compare patients with recovered LVEF with those who did not recover their LVEF.

We used a multivariate model to define the parameters associated with LVEF recovery: First, clinical and echocardiographic variables were adjusted to age and gender using binary logistic regression. Parameters that emerged significantly associated with the outcome were then stepwise introduced into the model of multivariate logistic regression. Kaplan–Meier survival analysis was used for survival curves. Event rates were compared using the log rank test. Cox analysis was performed to define the independent predictors of long-term mortality among baseline clinical and LVEF recovery.

Statistical significance was accepted at a two-sided $P < 0.05$. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA) and SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

BASELINE CHARACTERISTICS BY MODE OF PRESENTATION

Among the 91 study patients, 53 (58%) were defined as sub-acute onset cardiotoxicity and 38 (42%) as late-onset. The baseline clinical, electrocardiographic, and echocardiographic characteristics and the mode of presentation (heart failure or asymptomatic left ventricular dysfunction on a routine echo) are shown in Table 1. There were no significant differences in

Table 1. Baseline, clinical, electrocardiographic, and echocardiographic characteristics of the patients based on the mode of onset of cardiotoxicity

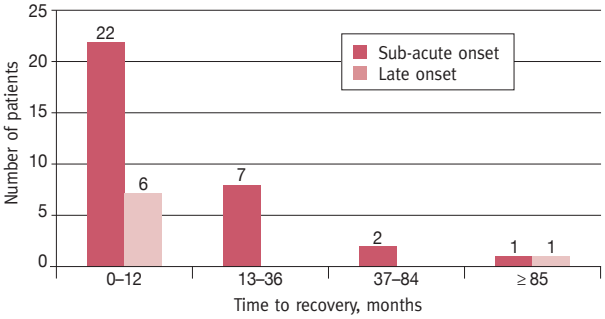
	Sub-acute onset cardiotoxicity n=53	Late-onset cardiotoxicity n=38	*P* value
Age, years*	59 ± 15	62 ± 15	0.35
Female gender	40 (76%)	28 (74%)	0.85
BMI, kg/m^2	25 ± 5	25 ± 5	0.89
CAD	7 (13%)	6 (16%)	0.73
Hypertension	16 (30%)	15 (40%)	0.357
Diabetes mellitus	8 (15%)	10 (26%)	0.185
AFIB	7 (13%)	6 (16%)	0.729
Solid tumors	34 (64%)	27 (71%)	0.490
Hematological malignancies	19 (36%)	11 (29%)	0.490
Adriamycin containing	44 (83%)	32 (89%)	0.92
Trastuzumab containing**	24 (45%)	2 (6%)	‹ 0.001
Radiation	20 (38%)	20 (56%)	0.097
Dyspnea	29 (56%)	26 (70%)	0.165
Fatigue	18 (35%)	13 (35%)	0.960
NYHA 3/4	16 (31%)	21 (57%)	0.014
Heart rate, beats/min*	83 ± 16	82 ± 15	0.649
LVEF (%)	37 ± 10	28 ± 8	‹ 0.001
LVEDD, mm	49.6 ± 7	54 ± 6.5	0.003
LVESD, mm	38 ± 7.5	44 ± 8	0.001
LAD, mm	37 ± 7.2	41 ± 7	0.012
PAP, mmHg	37 ± 12	41 ± 12	0.138
Severe diastolic dysfunction	10 (20%)	16 (44%)	0.017
Significant MR	9 (18%)	13 (34%)	0.092

*Continuous variables are reported as mean ± standard. Categorical variables are reported as numbers (%)

**22 patients had received combined treatment with adriamycin and trastuzumab, 20 of them were classified as sub-acute onset cardiotoxicity, 2 were defined as late-onset

AFIB = atrial fibrillation, BMI = body mass index, CAD = coronary artery disease, LVEF = left ventricular ejection fraction, LAD = left atrial diameter, LVEDD = left ventricular end diastolic dimension, LVESD = left ventricular end systolic dimension, MR = mitral regurgitation. NYHA = New York Heart Association functional classification, PAP = estimated systolic pulmonary artery pressure

Figure 1. Timing and number of patients with LVEF recovery according to presentation of cardiotoxicity (sub-acute, 53; late-onset, 38). Recovery of function occurred most often within 1 year but several cases of late recovery of left ventricular function were observed



LVEF= left ventricular ejection fraction

the two groups with regard to age, gender, or body mass index. Moreover, the type of onset of cardiotoxicity was not related to the presence of various co-morbidities or the type of malignancy (solid tumors vs. hematological malignancies). Patients with sub-acute onset were more likely to be treated with trastuzumab as part of their therapeutic regimen.

There was a higher prevalence of severe heart failure (NYHA > 2) among those with late-onset cardiotoxicity, while patients in the sub-acute group were more often detected during routine echocardiography. Accordingly, patients with sub-acute onset had a higher mean LVEF compared with those in the late-onset group (37% ± 10 vs. 28% ± 8%, respectively, $P < 0.001$).

PREDICTORS OF LVEF RECOVERY

Eighty-two patients (90%) had a second echocardiogram available for analysis. Of these, 39 (48%) improved their LVEF to ≥ 50%, whereas 43 (52%) did not recover their LVEF. Most of those patients who recovered their LVEF (n=28) did so within a period of 12 months from the diagnosis of cardiotoxicity [Figure 1]. However, there have been cases in which normalization of LVEF occurred more gradually, that is, over several years.

The baseline clinical and echocardiographic characteristics in relation to LVEF recovery are presented in Table 2. Patients with sub-acute onset more often recovered their LVEF compared to those with late-onset cardiotoxicity (65% vs. 22%, $P < 0.001$). Patients who recovered their LVEF were more often female, younger, and less likely to have diabetes mellitus. They also more often had solid tumors and received trastuzumab within their oncology regimen. They had a higher LVEF on diagnosis.

The only independent predictors of recovery were LVEF at diagnosis and trastuzumab therapy [Table 2]. Each percent increment in baseline LVEF was associated with an 8% increase in the likelihood for LVEF recovery. Trastuzumab therapy was associated with an approximate tenfold likelihood to recover cardiac function compared to other chemotherapeutic agents.

Table 2. Comparison of patients with cardiotoxicity based on recovered (LVEF ≥ 50%) or non-recovered ejection fraction

	Recovered LVEF n=39	Non-recovered LVEF n=43	*P* value	Multivariate HR, 95%CI, and *P* value
Age*	56 ± 14	64 ± 15	0.022	
Female gender	35 (90%)	26 (61%)	0.002	
BMI (kg/m²)	25 ± 5	26 ± 5	0.485	
CAD	4 (10%)	9 (19%)	0.186	
Hypertension	10 (26%)	18 (42%)	0.122	
Diabetes mellitus	4 (10%)	13 (30%)	0.03	
AFIB	5 (13%)	7 (16%)	0.658	
Solid tumors	31 (80%)	25 (58%)	0.038	
Hematological malignancies	8 (20%)	18 (42%)	0.038	
Sub-acute onset cardiotoxicity	32 (82%)	17 (40%)	< 0.001	
Adriamycin containing	32 (84%)	37 (88%)	0.614	
Trastuzumab containing	21 (55%)	2 (5%)	< 0.001	9.83, 1.74–55.4, 0.01
Radiation	17 (44%)	20 (48%)	0.716	
Dyspnea	19 (49%)	31 (76%)	0.013	
Fatigue	12 (31%)	13 (32%)	0.930	
NYHA 3/4	13 (32%)	23 (54%)	0.047	
Heart rate, beats/min*	83 ± 14	83 ± 14	0.878	
LVEF, %	37 ± 9	28 ± 9	< 0.001	1.08, 1.01–1.16 per 1% EF, 0.028
LVEDD, mm	49 ± 7	53 ± 7	0.002	
LVESD, mm	38 ± 8	43 ± 8	0.011	
LAD, mm	34 ± 5	41 ± 7	< 0.001	
PAP, mmHg	34 ± 11	42 ± 12	0.014	
Severe diastolic dysfunction	6 (17%)	17 (43%)	0.014	
Significant MR	4 (11%)	17 (41%)	0.004	

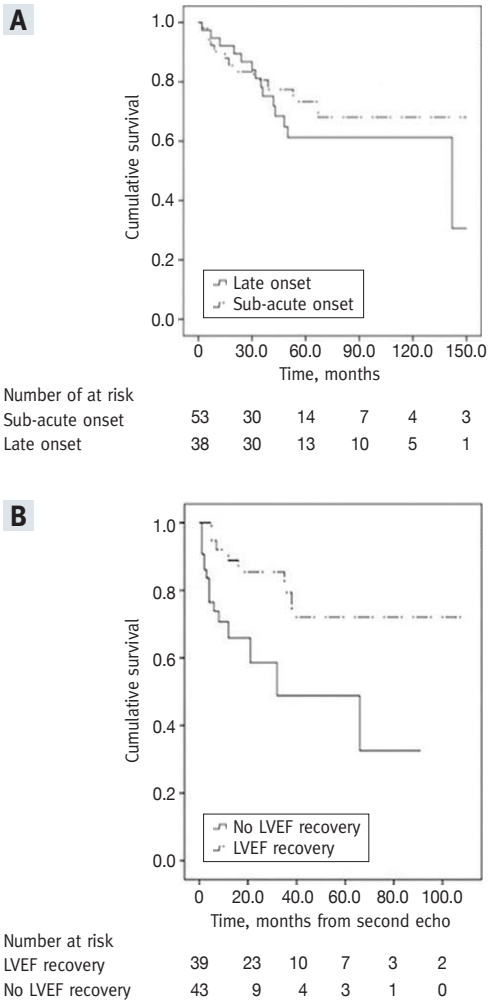
*Continuous variables are reported as mean ± standard. Categorical variables are reported as numbers (%)

95%CI = 95% confidence interval, AFIB = atrial fibrillation, BMI = body mass index, CAD = coronary artery disease, HR = hazard Ratios, LVEF = left ventricular ejection fraction, LAD = left atrial diameter, LVEDD = left ventricular end diastolic dimension, LVESD = left ventricular end systolic dimension, MR = mitral regurgitation: NYHA = New York Heart Association functional classification, PAP = pulmonary artery pressure

SURVIVAL

Over a mean follow-up of 4.5 years, all-cause mortality did not differ between patients with sub-acute vs. late-onset cardiotoxicity [Figure 2A]. Among the patients who recovered their systolic function, 7 (18%) patients died compared to 16 (37%) patients among those without LVEF recovery. The survival curves diverged early after the diagnosis and at the beginning

Figure 2. Kaplan–Meier survival estimates **[A]** There was no significant survival difference between sub-acute vs. late-onset cardiotoxicity (log rank test $P = 0.463$). **[B]** Landmark analysis based on LVEF recovery, showing an improved survival among those with LVEF recovery (log rank test $P = 0.005$)



LVEF= left ventricular ejection fraction

of therapy [Figure 2B]. Cox multivariate regression analysis (including age, gender, hematological type of malignancy, LVEF at diagnosis, and LVEF recovery) demonstrated that the absence of cardiac function recovery was the principal predictor of mortality in these patients (LVEF recovery hazard ratio = 0.17, 95% confidence interval 0.05–0.63, $P = 0.007$).

DISCUSSION

Effective chemotherapeutic regimens as well as biological agents provide treatment options and allow cure or long-term survival in many aggressive cancers. Limited data exist in the literature to guide clinicians on the natural history of cardiac dysfunction and LVEF recovery following cancer therapies.

The primary finding of our study was that almost half of the patients with cardiotoxicity recovered their LVEF. This finding is in agreement with our results of the general dilated cardiomyopathy cohort [10]. As previously reported [11-13], most of those who recovered their LVEF where treated with trastuzumab and/or were more likely to have a sub-acute mode of cardiotoxicity [Table 2]. Such patients are often diagnosed through periodic echocardiographic screening and have fewer symptoms and a lower incidence of left ventricular dysfunction. The time course for LVEF recovery ranged from 0 to 85 months, but the majority (72%) recovered during the first 12 months [Figure 1].

Recent studies by Cardinale et al. [14] and Thakur et al. [15] showed even higher rates of LVEF recovery ranging from 70% to 80%. Those results may arise from a different definition of improvement as well as a higher proportion of sub-acute cardiotoxicity detected by dedicated cardiology units closely associated with the oncology center. Non-invasive cardiac monitoring during the hazardous oncology treatment allows early detection and treatment of cardiotoxicity, leading in most cases to recovery of cardiac function [14,16,17].

We found that patients treated with trastuzumab are more likely to recover from left ventricular dysfunction once it develops. This finding is in line with results from previous studies [16,18,19], which indicated that cardiotoxicity resulting from trastuzumab is largely reversible. While trastuzumab-related cardiotoxicity appears to have a better prognosis, its reckless use may result in severe life-threatening heart failure. This complication typically occurs when trastuzumab is given following high dose anthracyclines or to an otherwise injured heart.

LVEF is the most important independent predictor of short- and long-term mortality in different cardiac conditions, including cardiac surgery, myocardial infarction, and ischemic and idiopathic cardiomyopathy [17,20-22]. Several studies have clearly demonstrated increased morbidity and mortality rates in patients with reduced LVEF, even when they are asymptomatic [20,21,23].

Our study cohort is representative of a general cardio-oncology population. The findings suggest that sub-acute onset and late-onset cardiotoxicity of oncotherapy may not constitute two distinct entities, but rather represent different stages of the same disease. Alternatively, late-onset cardiotoxicity may not be severe enough to be detected at the early stage but create increased susceptibility to myocardial injury by other triggers such as inflammation or pressure overload. The distinction depends not only on the definition but also on our ability to identify early sub-clinical cardiac damage. When the triggers for diagnosis are heart failure symptoms, which usually develop years after the exposure, then we most often define cardiotoxicity as late. However, if modern echo-Doppler follow-up protocols including tissue Doppler and strain imaging, are

used to monitor cardiac function, we are likely to diagnose the patient early, at the stage of asymptomatic LVEF reduction. Such patients would be defined as sub-acute cardiotoxicity and treated early [14]. These patients have a better response to therapy, which improves their cardiac function, often preventing the development of heart failure.

The prognosis of cardio-oncology patients is dependent on multiple variables and is only partly dependent on the mode of cardiotoxicity presentation [Figure 2A]. That finding could be attributed to numerous additional factors including co-morbidities and the original oncological disease. Apparently, the contemporary prognosis of these patients has markedly improved compared to two decades ago [24]. We think that both sub-acute and late-onset cardiotoxicity respond to the contemporary heart failure therapy. LVEF at diagnosis is an important and independent predictor of LVEF recovery in cardio-oncological patients [Table 2]. Patients who recovered their LVEF have a significantly reduced all-cause mortality [Figure 2B], a finding which is in line with previous studies [17,25].

LIMITATIONS OF THE STUDY

Limitations of our study include a partly retrospective design, a limited and small sample size (91 patients), the heterogeneity of the cancer diagnoses, and a large variability in follow-up duration. We are missing data on the exact composition and doses of chemotherapy to analyze the dose response relationship as well as various interactions. No rigorous echo-Doppler follow-up protocol was used but rather an individualized approach based on heart failure status and the requirements imposed by an ongoing oncological therapy. Yet, we believe that our observational data reflect a real-world situation.

CONCLUSIONS

Both sub-acute and late-onset cardiotoxicity appear to respond to contemporary heart failure therapy improving the prognosis of cardio-oncological patients. Early detection of cardiotoxicity is important to achieve LVEF recovery and prevent development of symptomatic heart failure, thereby reducing morbidity and mortality in oncological patients.

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