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Research Article

Echocardiographic Predictors of Cancer Therapeutics-Related Cardiac Dysfunction in Patients with Hematologic Malignancies

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Abstract

We aimed to identify the pre-treatment characteristics of patients who develop cancer therapeutics-related cardiac dysfunction (CTRCD) after treatment using various regimens involving chemotherapy, radiotherapy, and biologic therapy for hematologic malignancy. Among the 76 consecutive patients with hematologic malignancy who had complete transthoracic echocardiography data (left lateral decubitus and passive leg-lifting positions), clinical parameters, and cardiac biomarkers, five (6.6%) developed CTRCD after treatment. Three patients received allogeneic hematopoietic stem cell transplantation with total body irradiation for leukemia, while two received conventional chemotherapy. We examined approximately 40 clinical characteristics, biomarkers, and echocardiographic parameters for their ability to predict CTRCD in this population. Patients who developed CTRCD had significantly decreased diastolic wall strain at rest, as well as decreased ejection fraction and pulmonary venous systolic-to-diastolic flow ratio (S/D) during leg lifting (increased preload) on pre-treatment transthoracic echocardiography (P<0.05 for all). CTRCD was associated with pre-treatment liver dysfunction (P<0.05) but not with well-established biomarkers or risk factors. Our experience suggests that patients with left ventricular diastolic dysfunction before treatment may develop CTRCD, and that preload-induced changes on echocardiography may serve as CTRCD predictors.

Keywords: *cancer therapy, cardiotoxicity, cardiac dysfunction, predictive factor, echocardiography*

Introduction

Cancer treatment involves a combination of chemotherapy, radiotherapy, and surgery for curative or palliative purposes. However, many such treatments can cause cardiovascular complications including heart failure [1], which often have significant consequences on patient outcomes. Therefore, early detection and prediction of cancer therapeutics-related cardiac dysfunction (CTRCD) is crucial to the successful management of cancer patients with cardiovascular complications.

The evaluation of drug-induced cardiotoxicity has not been standardized. Changes in diastolic left ventricular (LV) function are observed early after anticancer therapy and are associated with a decrease in LV ejection fraction (LVEF) later on [2]. Echocardiographic indices for LV diastolic function, such as deceleration time of early diastolic filling (DcT), ratio of transmitral early LV filling velocity to early diastolic strain rate at the mitral annulus (E/e'), and the ratio of pulmonary venous systolic to diastolic flow, are dependent on preload changes, which, in turn, reflect reduced LV compliance and abnormal relaxation [3,4]. Cardiac biomarkers including B-type natriuretic peptide (BNP) [5], high-sensitivity cardiac troponin T (hs-TnT) and I [6], and high-sensitivity C-reactive protein (hs-CRP) [7] are commonly used for detection and monitoring of cardiotoxicity and may have prognostic value in identifying high-risk patients who would need closer follow-up. Additionally, ST2 has been shown to be a good marker of myocardial stretching [8], whereas pentraxin 3 has been shown to be a marker of inflammation [9]. In this study, we aimed to identify and report the echocardiographic and clinical characteristics of patients with CTRCD after treatment for hematologic malignancy.

Materials and Methods

This study included 76 consecutive patients who were treated for hematologic malignancies and underwent transthoracic echocardiography (TTE) before and after cancer treatment between January 2013 and December 2015 at the Institute of Medical Science of the University of Tokyo (Tokyo, Japan). TTE was performed using a CX50 system with a S5-1 transducer (Philips Medical Systems, Andover, MA, USA) and parameters were obtained in the left lateral decubitus and passive leg-lifting positions (with legs elevated to 45° from the horizontal position) [4,10]. CTRCD was diagnosed as a decrease in LVEF of ≥ 10% to <53%, according to relevant guidelines [11]. Plasma levels of ST2 and pentraxin 3 were measured using sandwich enzyme-linked immunosorbent assays according to the manufacturer's protocol (R&D Systems, Inc., Minneapolis, MN, USA). All patients underwent routine laboratory evaluations.

The data are presented as frequency (percentage) and median (range), as appropriate. The patients were stratified according to the incidence of CTRCD (with vs. without CTRCD). Between-group comparisons were conducted using the Mann-Whitney U-test. Categorical regression analysis was applied to identify the pre-treatment echocardiographic predictors of CTRCD. A P-value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). The study was approved by the institutional ethics committee of the Institute of Medical Science, and all patients provided written informed consent for having their data collected, used, and published for research purposes.

Results

Pre-treatment clinical characteristics

Of the 76 consecutive patients who received anti-cancer treatment for hematologic malignancy, five (6.6%) developed CTRCD. The median delay between the initiation of treatment and a diagnosis of CTRCD was 104 days (range, 73-116 days). The pre-treatment clinical parameters are summarized in Table 1. Among comorbidities, only elevation of transaminases was associated with CTRCD incidence. The frequency of previous anthracycline therapy and major underlying diseases of hematologic malignancy did not differ significantly between patients with and without CTRCD. The levels of cardiac biomarkers were not associated with CTRCD, with the exception of the plasma BNP levels, which showed weak association (P=0.058). Categorical regression analysis did not reveal any further clinical predictors of CTRCD. The clinical characteristics of the five patients who developed CTRCD are summarized in Table 2, whereas the detailed clinical histories are included in the Supplementary Information.

Table 1: Pre-treatment clinical parameters of patients receiving cancer therapeutics

Characteristic	Patients with CTRCD (n=5)	Patients without CTRCD (n=71)
Clinical characteristics		
Male sex	80%	62%
Age, years	47.0 [35.0–61.0]	54.5 [44.0–65.0]
BMI, kg/m^2	19.1 [18.2–24.8]	21.9 [20.0–24.1]
Hypertension	20%	24%
Diabetes mellitus	20%	13%
Dyslipidemia	40%	37%
CAD	0%	3%
Smoking history	40%	51%
Previous AC chemotherapy	60%	41%
Previous radiotherapy	0%	6%
Familial history of CAD	0%	13%
Cardiac biomarkers and blood test results		
BNP, pg/mL	32.5 [18.8–60.5]	17.3 [11.8–26.0]
High-sensitivity troponin T, pg/mL	3.8 [0.56–8.5]	4.5 [0.1–6.0]
High-sensitivity CRP, mg/dL	0.43 [0.05–8.38]	0.25 [0.06–1.88]
Pentraxin 3, ng/mL	4.0 [1.5–13.9]	1.4 [0.7–2.7]
ST2, pg/mL	15.2 [14.5–139.0]	18.2 [9.9–29.4]
Hemoglobin, g/dL	10.4 [8.3–14.7]	10.2 [8.6–12.4]
GOT, U/L	38.0 [33.0–75.0]*	22.0 [18.8–31.3]
GPT, U/L	38.0 [29.0–293.0]*	21.5 [13.8–36.8]
γ-GTP, U/L	46.0 [22.5–202.0]	39.0 [24.8–94.3]
Creatinine, mg/dL	0.77 [0.63–0.95]	0.66 [0.58–0.86]
eGFR, mL/min	84.0 [65.5–100.0]	81.0 [65.8–97.3]

Data shown as percentage or median [range], as appropriate between-group comparisons were conducted using the Mann-Whitney U-test.

*Statistically significant difference (P-value <0.05 was considered to indicate statistical significance and marked by an asterisk.

GOT: Glutamic Oxaloacetic Transaminase; GPT: Glutamic Pyruvic Transaminase; eGFR: estimated Glomerular Filtration Rate; BMI: Body Mass Index; AC: Anthracycline; CAD: Coronary Arterial Disease

Table 2: Baseline characteristics of patients who developed cancer therapeutics-related cardiac dysfunction

Patient No.	1	2	3	4	5
Age	44	47	26	56	66
Sex	M	F	M	M	M
Diagnosis	ALL	CML	AML	ATL	AL
Cumulative AC dose	380 mg/m^2	150 mg/m^2	108 mg/m^2	220 mg/m^2	75 mg/m^2
Previous RT	(-)	(-)	(-)	(-)	(-)
Underlying Heart Disease	(-)	(-)	(-)	(-)	mild AS
Hypertension	(-)	(-)	(-)	(-)	(+)
Diabetes Mellitus	(-)	(-)	(-)	(-)	(+)
Dyslipidemia	(+)	(-)	(-)	(-)	(+)
Liver Dysfunction	(-)	(-)	(-)	(+)	(+)
Smoking	former	(-)	current	(-)	(-)
Medication before cancer Tx*	(-)	(-)	(-)	(-)	(+)

*Medication for hypertension, diabetes mellitus, or dyslipidemia

ACs: Anthracycline; RT: Radiotherapy; Tx: Treatment; ALL: Acute Lymphocytic Leukemia; CML: Chronic Myeloid Leukemia; AML: Acute Myeloid Leukemia; ATL: Adult T-Cell Leukemia; AL: Acute Leukemia; AS: Aortic Stenosis

Pre-treatment echocardiographic characteristics

TTE parameters obtained in the left lateral decubitus and passive leg-lifting positions are summarized in Table 3. At rest, diastolic wall strain (DWS) was lower in patients with CTRCD than in those without CTRCD. During leg lifting, LVEF and pulmonary venous systolic-to-diastolic flow (S/D) ratio were lower in patients with CTRCD than in those without CTRCD. Other echocardiographic parameters for LV systolic and diastolic function were not associated with CTRCD incidence. Categorical regression analyses did not reveal any further echocardiographic predictors of CTRCD. Among the patients who developed CTRCD, the three were followed up to monitor cardiac function after introduction of angiotensin II receptor blockers (ARBs); in all three patients, LVEF improved to normal levels within 6 months of starting ARB therapy (Supplementary Information).

Table 3: Pre-treatment echocardiographic parameters of patients receiving cancer therapeutics

Characteristic	Patients with CTRCD (n=5)	Patients without CTRCD (n=71)
At rest		
LAVI, mL/m²	33.1 [21.1–49.3]	30.8 [254–40.1]
IVSd, mm	7.0 [6.9–7.4]	8.0 [7.0–9.0]
LVPWd, mm	8.0 [7.1–8.9]	8.0 [7.0–9.0]
LVDd, mm	50.0 [44.5–53.8]	48.0 [46.0–51.0]
LVDs, mm	33.0 [26.8–36.7]	30.0 [28.0–33.0]
SV, mL	99.6 [79.7–120.5]	90.2 [73.8–103.0]
EF, %	64.6 [61.5–69.2]	69.8 [66.7–73.5]
LVMI, g/m²	80.1 [75.7–88.4]	90.2 [78.5–107.3]
E/A ratio	0.94 [0.68–1.58]	1.03 [0.80–1.32]
DcT, ms	171.0 [157.0–200.0]	171.0 [153.0–193.0]
E/e' (averaged)	5.92 [5.77–11.71]	8.06 [6.71–9.60]
IRT, ms	63.0 [47.0–76.0]	63.0 [54.0–78.5]
Systolic PAP, mmHg	23.2 [21.0–26.0]	18.0 [16.0–23.0]
TAPSE, mm	21.7 [21.4–29.8]	24.6 [21.2–26.5]
S'TV, cm/s	14.1 [14.0–17.6]	13.8 [12.2–17.2]
DWS	0.35 [0.31–0.42]*	0.41 [0.38–0.44]
S/D ratio	1.53 [1.03–1.93]	1.37 [1.13–1.58]
During leg lifting		
LAVI, mL/m²	32.7 [27.0–36.1]	31.1 [26.9–36.6]
IVSd, mm	7.7 [7.6–8.8]	8.2 [7.5–8.8]
LVPWd, mm	8.4 [7.5–9.2]	8.4 [7.8–9.4]
LVDd, mm	46.2 [41.4–55.1]	48.6 [45.5–50.8]
LVDs, mm	30.3 [5.5–36.5]	29.9 [28.2–32.1]
SV, mL	98.8 [91.7–110.0]	88.8 [75.0–99.7]
EF, %	62.5 [59.2–67.0]*	70.1 [67.0–73.3]
LVMI, g/m²	78.1 [70.0–98.1]	94.8 [79.2–113.1]
E/A ratio	1.04 [0.69–1.55]	1.12 [0.92–1.28]
DcT, ms	153.0 [129.0–20.33]	162.0 [148.0–189.0]
E/e' (averaged)	6.23 [4.95–9.94]	7.69 [6.48–9.04]
IRT, ms	67.0 [49.5–78.5]	63.0 [54.0–72.0]
Systolic PAP, mmHg	18.5 [15.5–22.0]	16.6 [14.2–20.6]
TAPSE, mm	23.8 [23.2–32.2]	25.0 [22.0–28.0]
S'TV, cm/s	16.0 [14.0–18.9]	14.8 [13.2–16.2]
DWS	0.41 [0.34–0.45]	0.43 [0.38–0.48]
S/D ratio	1.23 [1.11–1.37]*	1.47 [1.30–1.58]

Data shown as percentage or median [range], as appropriate between-group comparisons were conducted using the Mann-Whitney U-test.

*Statistically significant difference (P-value <0.05 was considered to indicate statistical significance and marked by an asterisk.

LAVI: Left Atrial Volume Index; IVSd: Interventricular Septum diastole; LV: Left Ventricular; LVPWd: LV Posterior Wall at end-diastole; LVDd: LV Diastolic diameter; LVDs: LV Systolic diameter; SV: Stroke Volume; EF: Ejection Fraction; LVMI: LV Mass Index; E/A ratio: ratio of transmitral early to late LV filling velocity; DcT: Deceleration Time of early diastolic filling; E/e': Ratio of transmitral early left ventricular filling velocity to early diastolic Doppler tissue imaging of the mitral annulus; IRT: Isovolumetric Relaxation Time; PAP: Pulmonary Artery Pressure; TAPSE: Tricuspid Annular Plane Systolic Excursion; S'TV: velocity of systolic Doppler tissue imaging of the tricuspid annulus; DWS: Diastolic Wall Strain; S/D: Pulmonary venous systolic to diastolic flow ratio.

Discussion

Antineoplastic therapy is frequently complicated by cardiotoxicity [1]. Documented cardiovascular adverse events include LV dysfunction with resultant heart failure, conduction abnormalities, QT prolongation, coronary artery disease, venous thromboembolism, hypertension, and pulmonary arterial hypertension [1]. The purpose of this study was to clarify the echocardiographic and clinical characteristics of CTRCD in patients with hematologic malignancy. We compared the CTRCD and non-CTRCD patients in terms of pre-treatment clinical and echocardiographic characteristics to identify the predictors of CTRCD. Additionally, we provided an extensive description of each case involving CTRCD.

LV diastolic dysfunction early after anticancer therapy has been reported and seems to be associated with LV systolic dysfunction later on [2]. Preload increase due to leg lifting unmasks latent LV diastolic dysfunction [3,4]. In accordance with previous observations [4,12], we found that CTRCD was associated with decreased DWS at rest and decreased S/D ratio during leg lifting on pre-treatment TTE. The transmural myocardial strain profile (which reflects subtle LV fibrosis) during leg lifting was reported to be an effective predictor of subclinical LV dysfunction in patients with Duchenne muscular dystrophy and preserved LVEF [13]. We also found that decreased LVEF during leg lifting was associated with CTRCD, even though LVEF is known to increase during leg lifting in healthy subjects [10]. Thus, decreased LVEF during leg lifting may reflect latent LV myocardial dysfunction.

The underlying cardiovascular risk burden, which affects the incidence and severity of cardiovascular adverse events, often includes a history of hypertension, diabetes, prior cardiovascular disease, liver dysfunction, renal dysfunction, and prior chest radiation [14]. Among these risk factors, we only found liver dysfunction to be significantly associated with CTRCD, whereas other known risk factors including the cumulative dose of anthracycline did not exhibit significant association, likely due to the small sample of patients used for analysis (CTRCD, n=5; non-CTRCD, n=71).

Several sensitive and reproducible biomarkers of cardiac toxicity have been reported [6]. The most studied biomarkers include troponin and natriuretic peptides. In our patient, we measured ST2 and pentraxin 3 levels in addition to hs-TnT, BNP, and hs-CRP levels before and after chemotherapy. Although the plasma levels of BNP showed mild association with CTRCD (P=0.058), this trend was not significant. Further studies with large sample size are warranted to clarify the prognostic value of these biomarker levels for CTRCD.

ARBs may protect against CTRCD through direct inhibition of angiotensin II, as the local renin-angiotensin system plays a key role in CTRCD [15]. In our patients, ARBs helped recover impaired LVEF within 6 months of CTRCD onset (Supplementary Information). The CTRCD-protective effect of ARBs was previously reported in a randomized controlled trial enrolling patient with various malignancies [16]. Because ARBs sometimes induce symptomatic hypotension, especially in young patients, early introduction of ARBs upon CTRCD onset rather than pre-treatment with ARBs may be beneficial. In patients who develop CTRCD even after anthracycline treatment, LVEF recovery and

a reduction in the risk of cardiac events can be achieved if cardiac dysfunction is detected early and treatments are promptly initiated [17].

Our findings should be considered in the context of several limitations. First, only five patients developed CTRCD, limiting the extent and power of the statistical analysis. Second, while the cumulative dose of anthracycline did not differ between CTRCD and non-CTRCD patients, our sample included patients with various types of hematologic malignancies and treatment regimens, making it difficult to determine any specific associations of CTRCD with a certain type of malignancy, anti-cancer drug, or treatment regimen. Third, we did not evaluate global longitudinal strain, which is used to define subclinical LV dysfunction during and after cancer therapy [11].

Our present findings suggest that patients with decreased LV diastolic dysfunction or liver dysfunction before anti-cancer treatment should be carefully monitored for cardiac adverse effects. Routine TTE is recommended before and after anti-cancer treatment, with early introduction of ARBs if cardiac dysfunction is noted.

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Conflict of Interest

The authors declare that there are no conflicting interests with respect to the research, authorship, and/or publication of this article.

Ethics statement

The drafting of this report was approved by the institutional ethics committee of the Institute of Medical Science, and all patients provided written informed consent for having their data collected, used, and published for research purposes.

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