Prognostic Factors for Cancer Therapeutics-Related Cardiac Dysfunction in Breast Cancer Patients Treated with Current Anthracycline Regimens

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Abstract

Background

Anthracycline therapies cause myocardial damage and the onset of heart failure, depending on their doses. We investigated prognostic factors for cancer therapeutics-related cardiac dysfunction (CTRCD) in patients receiving modern anthracycline therapies.

Methods

Of 472 breast cancer patients with complete data treated with anthracycline, 8 were diagnosed with CTRCD.

Results

Multivariate regression analyses revealed that the anthracycline cumulative dose, concomitant use of molecular targeted drugs and a prechemotherapy left ventricular ejection fraction < 50% were independent and significant predictors of the onset of CTRCD.

Conclusions

Even in the modern era, the anthracycline cumulative dose is an independent risk factor for the onset of CTRCD.

Summary

In an investigation of prognostic factors for cancer therapeutics-related cardiac dysfunction (CTRCD) in breast cancer patients receiving modern anthracycline therapies, multivariate regression analyses revealed that the anthracycline cumulative dose, concomitant use of molecular targeted drugs and a prechemotherapy left ventricular ejection fraction < 50% remained independent and significant predictors of the onset of CTRCD.

Introduction

In 1977, von Hoff *et al.* reported a dose-dependent increase in anthracycline-induced cardiotoxicity.¹ A 5% increase in the risk of heart failure (HF) due to the use of doxorubicin at a dose of 400 mg/m² has been reported.² The American Society of Clinical Oncology (ASCO) defines a high dose as 250 mg/m² or more³, and in daily clinical practice, care is often taken not to exceed 250 mg/m² when developing a chemotherapy regimen. In addition, it is rare to use more than 400 mg/m² even if further administration is necessary depending on the patient's condition. Since some patients, however, experience cardiac

dysfunction even at doses of 100 mg/m² or less^{4, 5}, the current understanding is that there is no safe threshold.⁶ Echocardiography is essential for diagnosing cardiotoxicity, but in practice, it is difficult to perform repeated echocardiography, including before treatment initiation, during treatment and during follow-up, for all patients at all cancer treatment facilities. This strategy would be undesirable from the viewpoint of the appropriate use of medical resources. Therefore, the first step is to identify patients at high risk for cardiotoxicity based on the anticancer drug to be used. Currently, various guidelines have been published, reflecting the high level of interest in cardiotoxicity.^{3, 7–9} We investigated the prognostic factors for cancer therapeutics-related cardiac dysfunction (CTRCD) in Japanese breast cancer patients receiving modern anthracycline therapy.

Methods

The current study was a prospective, single-center, observational study that explored clinical outcomes in patients with breast cancer.

Study subjects

We prospectively investigated 625 consecutive patients who were diagnosed with breast cancer and received anthracycline therapy at Kumamoto University Hospital between January 2007 and December 2018. We recorded each patient's medical history and relevant clinical characteristics. We excluded 153 patients because of missing data, and the remaining 472 patients were enrolled in this study. The primary endpoint was the onset of CTRCD, which is described below in detail. The exact observation end date was December 31, 2020.

Clinical parameters

Baseline demographic data, cardiovascular risk factors, and medications on enrollment were documented. Hypertension was defined as blood pressure >140/90 mm Hg or taking antihypertensive medication, as previously described.^{10–12} Diabetes mellitus was defined as the presence of symptoms of diabetes and a casual plasma glucose concentration ≥ 200 mg/dL, a fasting plasma glucose concentration ≥ 126 mg/dL, and a 2-h plasma glucose concentration ≥ 200 mg/dL on the oral glucose tolerance test (75 g) or taking medication for diabetes mellitus. Dyslipidemia was defined as a low-density lipoprotein cholesterol concentration ≥ 140 mg/dL (≥ 3.63 mmol/L), a high-density lipoprotein cholesterol concentration < 40 mg/dL (1.04 mmol/L), or a triglyceride concentration ≥ 150 mg/dL (≥ 1.7 mmol/L). Blood samples were obtained under stable and fasting conditions in the early morning. Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m².¹³ The eGFR was calculated using the Japanese Society of Nephrology formula.¹⁴

Echocardiography

Echocardiography was performed as described in detail.¹⁵ In brief, echocardiography was performed using commercially available ultrasound equipment. The left ventricular ejection fraction was assessed

with the modified Simpson's method using apical two- and four chamber views. All sonographers were blinded to the patient's clinical history and data to minimize bias.

A decrease in the left ventricular ejection fraction (LVEF) >10 percentage points and to a value <53% was defined as CTRCD, according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging expert consensus.¹⁶ The utility of echocardiography in the detection of CTRCD was described in the expert consensus above.¹⁶ If LV dysfunction was not confirmed, echocardiography was performed every 3 months for the first 12 months and every 12 months thereafter based on the algorithm for the management of cardiotoxicity.¹⁷

Follow-up

After enrollment, the patients were followed up prospectively at outpatient clinics until an endpoint occurred. The primary endpoint was the onset of CTRCD described below in detail.

Statistical analysis

The Shapiro–Wilk test was used to assess the normality of the distribution of continuous data. Continuous variables with a normal distribution are expressed as the mean ± standard deviation, whereas those with skewed distributions are expressed as the median value with the interquartile range. Categorical data are presented as numbers or percentages. Differences between two groups were tested using Fisher's exact test or the χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables, as appropriate. We used the Kaplan–Meier method to estimate the primary endpoint probabilities and the log-rank test to compare the distributions of survival times among groups.

Univariate and multivariate Cox proportional hazards regression analyses were used to estimate the hazard ratios (HRs) for the onset of CTRCD. We selected variables that were statistically significant in the univariate analyses ($P < 0.05$) for inclusion in the multivariate analyses (Model 1). Then, we performed multivariate analyses using the factors listed in various recent guidelines.^{3,7–9} A P -value <0.05 was considered to denote statistical significance. Statistical analyses were performed using SPSS version 26 (IBM Inc., Armonk, NY, USA).

Results

The baseline characteristics of the patients are shown in Table 1. The observation period was 92.1 ± 49.4 (mean ± standard deviation) months, and the anthracycline cumulative dose in all patients was 248.5 ± 54.0 mg/m² (doxorubicin-converted dose). Eight patients were clinically diagnosed with CTRCD (1.69%). The CTRCD (+) group had a higher anthracycline cumulative dose and a higher proportion of patients receiving concomitant immune/targeted therapy than the CTRCD (-) group ($P=0.010$ and $P=0.020$, respectively). The prevalence of hypertension was significantly higher in the CTRCD (+) group ($P=0.040$). The prechemotherapy LVEF was significantly lower in the CTRCD (+) group ($P=0.001$). There were no significant differences between the two groups with regard to age, the use of radiation therapy or the prevalence of diabetes mellitus and dyslipidemia. The results of the Cox proportional hazards regression

analyses are shown in Table 2. Univariate logistic regression analyses identified the anthracycline cumulative dose (HR: 1.02, 95% confidence interval (CI): 1.01-1.03, $P=0.001$), concomitant immune/targeted therapy (HR: 5.25, 95% CI: 1.06-26.02, $P=0.042$), prechemotherapy LVEF (HR: 0.86, 95% CI: 0.79-0.94, $P=0.001$) and prechemotherapy LVEF < 50% (HR: 12.96, 95% CI: 1.59-105.78, $P=0.017$) as significant factors associated with the onset of CTRCD. Multivariate Cox proportional regression analyses including the abovementioned significant factors from the univariate analyses identified the anthracycline cumulative dose, concomitant immune and targeted therapies and prechemotherapy LVEF < 50% as independent predictors of the onset of CTRCD (HR: 1.03, 95% CI: 1.01-1.04, $P=0.001$, HR: 28.39, 95% CI: 1.13-713.66, $P=0.042$ and HR: 269.71, 95% CI: 6.30-11551.50, $P=0.004$, respectively). In the same manner, multivariate regression analyses (Models 2-5) identified the anthracycline cumulative dose as an independent predictor of the onset of CTRCD. A receiver operating characteristic curve was constructed to assess the ability of the anthracycline cumulative dose to predict the onset of CTRCD (figures not shown). The area under the curve for the anthracycline cumulative dose was 0.626 (95% CI: 0.461-0.790, $P=0.223$). When the cutoff value for the anthracycline cumulative dose was used (242.61 mg/m²), the sensitivity and specificity were 100% and 32.8%, respectively, for the detection of the onset of CTRCD.

Discussion

The development and advancement of cancer chemotherapeutic agents have been remarkable, and with the advent of molecularly targeted drugs and immune checkpoint inhibitors and the diversification of treatment regimens, the survival time of cancer patients has been extended, and the population of cancer survivors is expanding. CTRCD is the most important consideration when determining the prognosis of cancer patients receiving treatment and is a new clinical issue. In particular, the onset of HF due to cancer chemotherapy is a serious complication that results in substantial decreases in the odds of a favorable prognosis and patient quality of life after the completion of cancer treatment. There are many aspects of the mechanism of chemotherapy-induced HF that remain unclear; however, the management of cardiac dysfunction/HF induced by chemotherapy is based on the identification of patients who are at high risk and predicting the onset of HF during chemotherapy. The need for high-quality evidence that can be used to achieve an early diagnosis/early treatment is an urgent issue.

In the present study, our results demonstrated that the anthracycline cumulative dose, concomitant immune/targeted therapy and prechemotherapy LVEF < 50% were independent and significant predictors of the onset of CTRCD. Moreover, we identified the clinical features of CTRCD patients, although the cohort was small. Interestingly, the 3 abovementioned variables that were related to the onset of CTRCD were baseline patient characteristics at the time of enrollment (Table 1). Furthermore, our study revealed an anthracycline cumulative dose threshold for the onset of CTRCD of 243 mg/m². This threshold is highly consistent with the ASCO recommendation of 250 mg/m².³

It is important for this information to be freely shared, and it should be included in educational materials for medical professionals. Moreover, it is essential for oncologists and cardiologists to be aware of this information.

Study Limitations

The present study has several limitations. First, this study was a single-center study with a very small sample size. Therefore, a larger multicenter study with patients of multiple ethnicities is needed. Second, the possibility of underdiagnosis due to the lack of follow-up echocardiography cannot be ruled out. In addition, patients were diagnosed based on their LVEF alone and were not evaluated based on diagnostic criteria involving global longitudinal strain values. Third, the cause of the onset of HF is not always the effect of anticancer drugs. Furthermore, it is unclear which factors and to what extent these factors contribute to the prognosis of CTRCD. Hence, further pathophysiological and molecular physiological studies, including animal experiments, are warranted. Additional detailed, large-scale clinical studies may be needed to verify our findings.

Conclusions

Despite these limitations, we clearly identified the prognostic factors for CTRCD in breast cancer patients treated with current anthracycline regimens. Although there are many factors that affect the prognosis of cancer patients and multicenter, large-sample studies are needed to confirm the prognostic value of these variables in cancer patients, our results provide substantial insights into prognostic prediction in cancer patients.

Declarations

Ethical Approval and Consent to participate

All procedures were conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the Institutional Review Board of Kumamoto University (Approval number, Rinri 1858). This study is registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000047554). Opt-out materials are available at: <https://kumadai-junnai.com/wp-content/uploads/kcancer.pdf>

Consent for publication

Not applicable.

Availability of data and materials

The data underlying this article will be shared on reasonable request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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Disclosure

All authors have nothing to disclose.

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Tables

Table 1
Baseline characteristics of enrolled patients

	All patients (n = 472)	CTRCD (-) (n = 464)	CTRCD (+) (n =8)	Pvalue
Age, years	53.0 ± 11.0	53.1 ± 11.0	51.4 ± 10.6	0.667
BMI, kg/m ²	23.1 ± 3.9	23.1 ± 4.0	23.4 ± 2.7	0.822
BSA, m ²	1.54 ± 0.13	1.54 ± 0.13	1.52 ± 0.10	0.789
Breast cancer profile				
Cancer stage				
- 0-III (%)	83 (18)	81 (17)	2 (25)	0.579
- II-IV (%)	386 (82)	380 (82)	6 (75)	0.617
- Unknown (%)	3 (1)	3 (1)	0 (0)	0.820
Chemotherapy*				
- FEC (%)	261 (55)	257 (55)	4 (50)	0.762
- EC (%)	163 (35)	159 (34)	4 (50)	0.355
- AC, FAC (%)	43 (9)	42 (9)	1 (13)	0.737
- Others (%)	6 (1)	6 (1)	0 (0)	0.747
Anthracycline dose [†] , mg/m ²	248.5 ± 54.0	247.7 ± 53.0	297.5 ± 86.8	0.010
Molecular target therapy [‡]				
- Trastuzumab (%)	148 (31)	142 (31)	6 (75)	0.007
- Bevacizumab (%)	18 (4)	18 (4)	0 (0)	0.571
- Pertuzumab (%)	13 (3)	9 (2)	4 (50)	0.038
- Lapatinib (%)	0 (0)	0 (0)	0 (0)	-
Radiation therapy (%)	107 (23)	106 (23)	1 (13)	0.315

Data are presented as the mean ± SD, or number (percentage).

CTRCD, cancer therapeutics-related cardiac dysfunction; BMI, body mass index; BSA, body surface area; FEC, fluorouracil, epirubicin, and cyclophosphamide; EC, epirubicin and cyclophosphamide; AC; doxorubicin and cyclophosphamide; CKD, chronic kidney disease; LVEF, left ventricle ejection fraction; BNP, brain natriuretic peptide

* Overlaps possible †Doxorubicin converted dose

	All patients (n = 472)	CTRCD (-) (n = 464)	CTRCD (+) (n = 8)	P value
Cardiovascular risk profile				
Hypertension (%)	131 (30)	126 (27)	5 (63)	0.040
Diabetes mellitus (%)	111 (24)	110 (24)	1 (13)	0.345
Dyslipidemia (%)	18 (4)	17 (4)	1 (13)	0.515
CKD (%)	30 (6)	30 (6)	0 (0)	0.425
Prechemotherapy LVEF, %	65.0 ± 4.4	65.1 ± 4.2	60.1 ± 8.2	0.001
Prechemotherapy BNP, pg/mL	23.8 ± 33.6	22.6 ± 30.4	60.1 ± 92.4	0.555
Observation periods, month	92.1 ± 49.4	93.1 ± 49.0	33.9 ± 34.0	0.001
Early < 12 months	-	-	3 (38)	-
Late ≥ 12 months	-	-	5 (63)	-
Data are presented as the mean ± SD, or number (percentage).				
CTRCD, cancer therapeutics-related cardiac dysfunction; BMI, body mass index; BSA, body surface area; FEC, fluorouracil, epirubicin, and cyclophosphamide; EC, epirubicin and cyclophosphamide; AC, doxorubicin and cyclophosphamide; CKD, chronic kidney disease; LVEF, left ventricle ejection fraction; BNP, brain natriuretic peptide				
* Overlaps possible †Doxorubicin converted dose				

Due to technical limitations, table 2 is only available as a download in the Supplemental Files section.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table2a.png](#)
- [Table2b.png](#)