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ORIGINAL PAPER

Recovery from left ventricular dysfunction was associated with the early introduction of heart failure medical treatment in cancer patients with anthracycline-induced cardiotoxicity

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Abstract

Background Left ventricular (LV) dysfunction due to anthracycline-induced cardiotoxicity (AIC) has been believed to be irreversible. However, this has not been confirmed and standard medical treatment for heart failure (HF) including renin–angiotensin inhibitors and β-blockers may lead to its recovery.

Methods and results We thus retrospectively studied 350 cancer patients receiving anthracycline-based chemotherapy from 2001 to 2015 in our institution. Fifty-two patients (14.9%) developed AIC with a decrease in LV ejection fraction (LVEF) of 24.1% at a median time of 6 months [interquartile range (IQR) 4–22 months] after anthracycline therapy. By multivariate analysis, AIC was independently associated with cardiac comorbidities including ischemic heart disease, valvular heart disease, arrhythmia, and cardiomyopathy [odds ratio (OR) 6.00; 95% confidence interval (CI) 2.27–15.84, $P=0.00044$), lower baseline LVEF (OR per 1% 1.09; 95% CI 1.04–1.14, $P=0.00034$). During the median follow-up of 3.2 years, LV systolic dysfunction recovered among 33 patients (67.3%) with a median time of 4 months (IQR 2–6 months), which was independently associated with the introduction of standard medical treatment for HF (OR 9.39; 95% CI 2.27–52.9, $P=0.0014$) by multivariate analysis.

Conclusion Early initiation of standard medical treatment for HF may lead to LV functional recovery in AIC.

Keywords Anthracycline · Cardiotoxicity · Heart failure · Medical treatment

Introduction

Advances in chemotherapeutic agents have significantly improved the survival rates of cancer patients. Anthracyclines are effective anti-neoplastic agents and remain the mainstay of treatment in a wide variety of hematological and solid organ malignancies including leukemia, lymphoma, breast cancer, and soft tissue sarcoma [1, 2]. Their anti-neoplastic effect, however, is hindered by the development of cardiotoxicity which negatively impacts clinical outcomes and limits oncological therapeutic options in cancer patients [3]. The most common clinical presentation of cardiotoxicity induced by anthracyclines is a dose-dependent cardiomyopathy which leads to heart failure (HF) and its prognostic implication is devastating [4].

Anthracycline-induced cardiotoxicity (AIC) is now increasingly well-recognized with the improvement in cancer survivorship and complexed with the greater opportunity to use in conjunction with newly developed anti-neoplastic agents targeting to specific growth signaling pathways and may affect the heart. Combinational therapy with other chemotherapeutic agents equipped with potential cardiotoxicity and chest radiotherapy often amplifies cardiotoxicity and represents multifactorial nature and clinical course in patients with AIC. Apart from the direct cardiotoxic effects of the anthracycline, the growing concern for potential cardiotoxicity could lead to a dose reduction or premature

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cessation of anthracyclines and a change to less-effective second-line agents, which may also adversely affect survival.

Although the specialized new field of cardio-oncology which provides an interdisciplinary collaboration between oncologists and cardiologists has evolved, there are still limited data regarding the occurrence and prognosis of AIC and appropriate management of these patients [5, 6]. As a consequence, such uncertainty greatly undermines the decision making of clinicians to provide or tailor the appropriate chemotherapy regimens.

AIC was traditionally considered to have a poor prognosis [4] and be refractory to old standard HF therapy including only digoxin and diuretics. The efficacy of current standard HF therapy such as renin–angiotensin inhibitors and β−blocker remains unsolved. Although AIC was believed to be irreversible [7] and could lead to progressive end-stage HF [8], recent studies have suggested that the reduction in left ventricular ejection fraction (LVEF) can be recovered when it is detected early and timely intervention is initiated [9, 10]. Accordingly, it is of clinical importance to identify clinical predictors associated with the prevention or recovery of AIC among patients treated with the anthracycline.

We therefore retrospectively investigated the occurrence and predictors of AIC and LVEF recovery from AIC, and its association with the introduction of standard HF therapy.

Methods

Study population

With Institutional Review Board approval, a retrospective study using the echocardiography laboratory software was performed and consecutive patients (age ≥ 15 years) who underwent anthracycline-based chemotherapy from January 1, 2001, to December 31, 2015, and received serial echocardiographic assessments before and after the chemotherapy. Patients treated with anthracycline followed by trastuzumab were excluded.

Cardiac evaluation and definition of AIC

Two-dimensional transthoracic echocardiograms were reviewed by two independent investigators. The LV cavity dimensions and LVEF were measured from the modified biplane Simpson's method. Any discordance between the readers was resolved by consensus. Cardiotoxicity was defined as a decrease in the LVEF of > 10%, to a value < 53% based on the recently published consensus and most used definitions [11]. These declines in LVEF were confirmed by a repeated echocardiogram taken at a few weeks interval. The decline in LVEF derived from other causes such as sepsis was excluded.

Recovery of LV systolic function was defined as an increase in LVEF of > 10% from the nadir but remaining > 5% below baseline (partial recovery) or an increase in LVEF of > 10% from the nadir to within 5% of baseline (full recovery). No recovery of LV systolic function was defined as an increase in LVEF of < 10% from the nadir and remaining > 5% below baseline [11].

Data collection

Clinical data on age, gender, cancer diagnosis, past medical history, coronary risk factors including hypertension, diabetes mellitus, dyslipidemia, smoking, cardiac comorbidities including ischemic heart disease, valvular heart disease, arrhythmia, and congenital heart disease, chemotherapy regimen and agents with attention to anthracyclines, radiation therapy to the left chest, and concomitant medications, cardiac intervention, completion of planned chemotherapy were retrieved. The dose of anthracyclines was converted to doxorubicin equivalent dose according to conversion formulas [12]. Follow-up information was obtained through a review of the institutional electronic medical records. Etiology of HF was investigated and all cardiovascular events were defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

Statistical analysis

Categorical data are presented as numbers with percentages and comparison between categorical variables was analyzed using the Chi square test or Fisher's exact test as appropriate. Continuous data which are not normally distributed are presented as medians with first and third quartiles, and data which are normally distributed are presented as a mean and standard deviation. Comparison between continuous variables was assessed using Student's *t* test or Mann–Whitney *U* test, as appropriate. Time to cardiotoxicity was calculated using the Kaplan–Meier method and compared by log-rank test. Multivariable logistic regression analysis with a stepwise selection of variables was used to determine the association of clinical and echocardiographic variables with the occurrence of AIC. Covariates with a *P* value of less than 0.10 in the univariate analysis and predefined baseline covariates were included: age, gender, cardiac comorbidities, left chest radiation therapy, cumulative anthracycline dose, LVEF. LVDd, LVDs, LVEDVI, and LVESVI were excluded as they were correlated with LVEF. The association of demographic, clinical and echocardiographic parameters with the reversibility of AIC was also determined using multivariable logistic regression analysis. Covariates with a *P* value of less than 0.10 in the univariate analysis as well as clinically relevant variables were included in multivariate analysis. LVEF at cardiotoxicity was excluded among

potential independent predictors as it was strongly associated with the introduction of HF medication. Candidate variables were age, cardiac disease, cumulative anthracycline dose, and HF medications. All probability values were two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed with the use of JMP statistical package and GraphPad Prism.

Results

Patient characteristics

This study consists of 350 cancer patients (189 men) treated by anthracycline, with a mean age of 50 years. They had lymphoma (52.3%), leukemia (28.9%), sarcoma (11.4%), and breast cancer (2.6%). The concomitant chemotherapy was as follows; alkylating agent 81.4%, antimetabolite 60.6%, microtubule-targeting agent 68.9%, topoisomerase inhibitor 37.4%, platinating agent 26.0%, molecularly targeted drug 44.9%, antitumor antibiotic 9.4%, and hormone drug 61.7%. The median periods of follow-up after the first and last anthracycline administration were 3.5 years (IQR 1.8–5.4 years) and 2.6 years (IQR 1.0–4.8 years), respectively.

Clinical characteristics of AIC

Fifty-two patients (14.9%) developed AIC. Their oncological disease included lymphoma (46.1%), leukemia (32.7%), sarcoma (9.6%), and breast cancer (3.8%). Thirty-four patients (65.4%) were in New York Heart Association (NYHA) class I or II, and 18 (34.6%) were in class III or IV. All the patients who presented with NYHA class III or IV were hospitalized due to acutely decompensated heart failure (ADHF). The AIC occurred at a median of 6 months (IQR 4–22 months) after first anthracycline therapy (Fig. 1a). Forty-four patients (84.6%) developed AIC within the first year after the completion of anthracycline therapy. Twenty-nine patients (55.8%) required dose reduction or premature discontinuation of anthracyclines and changed to non-anthracycline agent usage. The LVEF was $64.9 \pm 9.3\%$ at baseline and $40.2 \pm 11.1\%$ at the diagnosis of AIC (Fig. 1b). Of note, the LVEF after chemotherapy even in patients who did not develop AIC was lower than that at the baseline ($64.4 \pm 6.3\%$ vs $69.7 \pm 6.7\%$, $P < 0.0001$).

The clinical characteristics of patients with or without the development of AIC are summarized in Table 1. Univariate analysis revealed that cardiac comorbidities, cumulative anthracyclines' dose, LVDd/Ds, LVEDVI/ESVI, LVEF, and IVS were associated with the development of AIC. No significant differences in terms of other cardiovascular risk factors or left chest radiation therapy were observed.

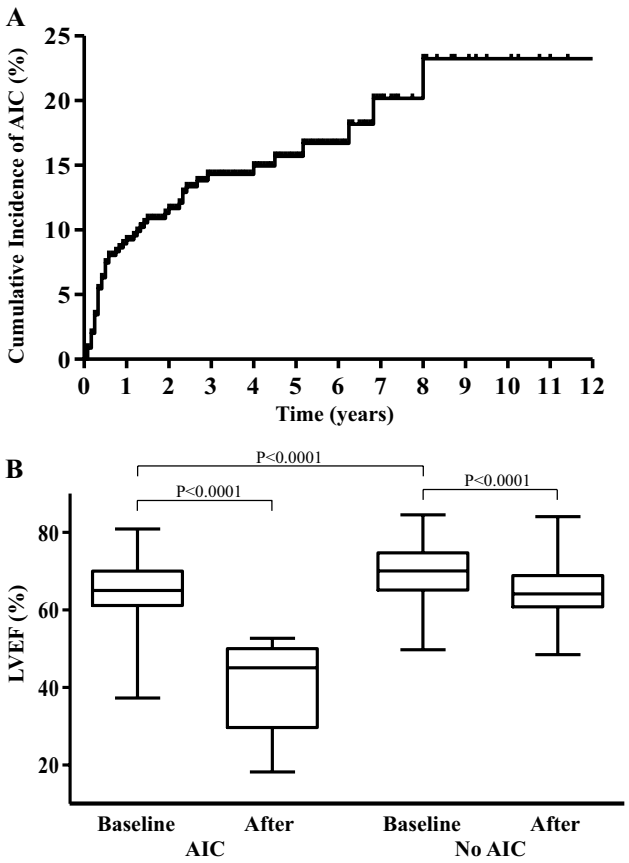

Fig. 1 **a** Cumulative incidence of anthracycline-induced cardiotoxicity (AIC) after first anthracycline therapy. **b** Time-dependent changes of left ventricular ejection fraction (LVEF) at baseline and after chemotherapy for patients with AIC or No AIC. Box-plot values are expressed as the median (horizontal line in each box) and 25th and 75th percentiles (top and bottom of each box), with whiskers (top and bottom of each bar) drawn to the minimum and maximum values

By multivariate analysis, cardiac comorbidities [the odds ratio (OR) 6.00; 95% confidence interval (CI) 2.27–15.84, $P = 0.00044$] and lower baseline LVEF (OR per 1% 1.09; 95% CI 1.04–1.14, $P = 0.00034$) were identified to be independently associated with AIC (Table 2).

During the median follow-up of 3.5 years, 133 (38.0%) patients died. One hundred and twenty-nine (97.0%) patients died of tumor-related causes, 4 (2.6%) of sepsis, but no cardiac death was identified. When stratified by AIC, cumulative all-cause mortality rates were not significantly different between patients who did or did not develop AIC (Fig. 2).

Recovery from LV systolic dysfunction

Twenty-seven out of 52 patients (51.9%) who developed AIC had HF medications including renin–angiotensin inhibitors or β-blocker. Thirteen out of 29 asymptomatic patients (44.8%) with AIC did not receive such

Table 1 Baseline demographic, clinical, and echocardiographic characteristics of the patients who did or did not develop anthracycline-induced cardiotoxicity (AIC)

Characteristics	Total $N=350$	AIC $N=52$	No AIC $N=298$	P value
Demographics				
Age at anthracycline treatment, year	50 ± 16	48 ± 16	50 ± 16	0.47
Female	161 (46.0)	30 (58.0)	131 (44.0)	0.07
Body surface area, m^2	1.62 ± 0.19	1.60 ± 0.17	1.62 ± 0.19	0.43
Cardiovascular risk factors				
Hypertension	55 (15.7)	7 (13.5)	48 (16.1)	0.84
Diabetes mellitus	34 (9.7)	4 (7.7)	30 (10.1)	0.80
Hypercholesterolemia	30 (8.6)	4 (7.7)	26 (7.9)	> 0.99
Current or past smoker	126 (36.0)	22 (42.3)	104 (34.9)	0.35
Cardiac comorbidities	39 (11.1)	13 (25.0)	26 (8.7)	0.0016
Ischemic heart disease	14 (4.0)	3 (5.8)	11 (3.7)	
Valvular heart disease	8 (2.3)	2 (3.8)	6 (2.0)	
Arrhythmia	12 (3.4)	7 (13.5)	5 (1.7)	
Cardiomyopathy	2 (0.6)	1 (1.9)	1 (0.3)	
Congenital heart disease	2 (0.6)	0 (0)	2 (0.7)	
Pericardial disease	2 (0.6)	0 (0)	2 (0.7)	
Oncological disease				0.68
Lymphoma	183 (52.3)	25 (48.1)	158 (53.0)	
Leukemia	101 (28.9)	18 (34.6)	83 (27.9)	
Sarcoma	40 (11.4)	5 (9.6)	35 (11.7)	
Breast	9 (2.6)	2 (3.8)	7 (2.3)	
Myeloma	5 (1.4)	0 (0)	5 (1.7)	
Others	12 (3.4)	2 (3.8)	10 (3.4)	
Left chest radiation therapy	138 (39.4)	21 (40.4)	117 (39.3)	0.88
Anthracycline				
Doxorubicin	197 (56.3)	28 (53.8)	169 (56.7)	0.76
Idarubicin	29 (8.3)	3 (5.8)	26 (8.7)	0.60
Pirarubicin	18 (5.1)	4 (7.7)	14 (4.7)	0.32
Daunorubicin	7 (2.0)	2 (3.8)	5 (1.7)	0.28
Epirubicin	7 (2.0)	0 (0)	7 (2.3)	0.60
Aclarubicin	3 (0.9)	0 (0)	3 (1.0)	> 0.99
Pegylated liposomal doxorubicin	3 (0.9)	0 (0)	3 (1.0)	> 0.99
Doxorubicin + idarubicin	1 (0.3)	1 (1.9)	0 (0)	0.15
Doxorubicin + idarubicin + aclarubicin	1 (0.3)	0 (0)	1 (0.3)	> 0.99
Doxorubicin + pirarubicin	9 (2.6)	1 (1.9)	8 (2.7)	> 0.99
Doxorubicin + daunorubicin	3 (0.9)	0 (0)	3 (1.0)	> 0.99
Doxorubicin + daunorubicin + mitoxantrone	6 (1.7)	2 (3.8)	4 (1.3)	0.22
Doxorubicin + epirubicin	1 (0.3)	0 (0)	1 (0.3)	> 0.99
Doxorubicin + mitoxantrone	13 (3.7)	0 (0)	13 (4.4)	0.23
Idarubicin + pirarubicin + mitoxantrone	1 (0.3)	1 (1.9)	0 (0)	0.15
Idarubicin + daunorubicin	10 (2.9)	2 (3.8)	8 (2.7)	0.65
Idarubicin + daunorubicin + mitoxantrone	12 (3.4)	4 (7.7)	8 (2.7)	0.086
Idarubicin + daunorubicin + mitoxantrone + aclarubicin	1 (0.3)	0 (0)	1 (0.3)	> 0.99
Idarubicin + epirubicin	1 (0.3)	0 (0)	1 (0.3)	> 0.99
Idarubicin + epirubicin + aclarubicin	1 (0.3)	0 (0)	1 (0.3)	> 0.99
Idarubicin + aclarubicin	2 (0.7)	0 (0)	2 (0.7)	> 0.99
Idarubicin + mitoxantrone	5 (1.4)	0 (0)	5 (1.7)	> 0.99
Pirarubicin + mitoxantrone	1 (0.3)	0 (0)	1 (0.3)	> 0.99

Table 1 (continued)

Characteristics	Total $N=350$	AIC $N=52$	No AIC $N=298$	P value
Pirarubicin + actinomycin D	1 (0.3)	0 (0)	1 (0.3)	> 0.99
Daunorubicin + mitoxantrone	17 (4.9)	4 (7.7)	13 (4.4)	0.30
Cumulative doxorubicin equivalent dose, mg/m^2	260 ± 120	300 ± 132	260 ± 118	0.025
Concomitant chemotherapy				
Alkylating agent	285 (81.4)	42 (80.8)	243 (81.5)	0.85
Antimetabolites	212 (60.6)	31 (59.6)	181 (60.7)	0.88
Microtubule-targeting agent	241 (68.9)	34 (65.4)	207 (69.5)	0.63
Topoisomerase inhibitor	131 (37.4)	17 (32.7)	114 (38.3)	0.54
Platinating agent	91 (26.0)	15 (28.8)	76 (25.5)	0.61
Molecular-targeted drug	157 (44.9)	24 (46.2)	133 (44.6)	0.88
Antitumor antibiotics	33 (9.4)	8 (15.4)	25 (8.4)	0.12
Hormone drug	216 (61.7)	32 (61.5)	184 (61.7)	> 0.99
Others	15 (4.3)	5 (9.6)	10 (3.4)	0.056
Medication for pre-existing disease				
ACE inhibitor or ARB	29 (8.3)	4 (7.7)	25 (7.5)	> 0.99
β-Blocker	17 (4.9)	4 (7.7)	13 (3.9)	0.30
Statin	30 (8.6)	4 (7.7)	26 (7.9)	> 0.99
Echocardiographic parameters				
LVDd, mm	46.8 ± 5.0	48.3 ± 6.1	46.6 ± 4.8	0.049
LVDs, mm	28.5 ± 4.5	31.3 ± 6.7	28.0 ± 4.0	< 0.0001
LVEDVI, mL/m^2	63.6 ± 14.1	70.0 ± 18.2	62.3 ± 13.3	0.0028
LVESVI, mL/m^2	19.8 ± 7.7	25.8 ± 13.1	18.7 ± 6.1	< 0.0001
LAD, mm	34.1 ± 6.6	35.4 ± 10.8	33.9 ± 5.8	0.22
LVEF, %	69.1 ± 7.2	64.9 ± 9.3	69.7 ± 6.7	< 0.0001
IVS, mm	8.5 ± 1.3	8.1 ± 1.2	8.6 ± 1.4	0.021
PW, mm	8.7 ± 1.5	8.2 ± 1.0	8.7 ± 1.6	0.054
E, cm/s	72.4 ± 20.4	75.0 ± 23.4	72.0 ± 20.0	0.42
E/*A*	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.5	0.81
DT, ms	187.0 ± 43.5	164.2 ± 34.9	186.4 ± 44.3	0.0010
Septal *e*′, cm/s	8.2 ± 2.7	8.5 ± 2.3	8.2 ± 2.7	0.42
E/*e*′	9.4 ± 3.6	9.6 ± 4.9	9.4 ± 3.4	0.70
s′	8.1 ± 1.6	8.0 ± 1.7	8.2 ± 1.6	0.45
IVC, mm	13.6 ± 3.3	13.6 ± 4.4	13.5 ± 3.1	0.94

Data are presented as number (%) of patients or median (quartiles 1–3)

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *LVDd* left ventricular diastolic diameter, *LVDs* left ventricular systolic diameter, *LVEDVI* left ventricular end-diastolic volume index, *LVESVI* left ventricular end-systolic volume index, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction, *DT* deceleration time

medications. In 3 out of 52 AIC patients, subsequent evaluation of LVEF was not available. Recovery of LV systolic dysfunction occurred in 33 (67.3%) patients with median time to recovery of 4 months (IQR, 2 to 6 months). Thirteen patients (26.5%) were fully and 20 (40.8%) patients were partially recovered. The LVEF of those who recovered were 64.3 ± 9.8%, 36.8 ± 11.6%, and 56.9 ± 8.4% at baseline, AIC, and follow-up, respectively. The LVEF of those who did not recover were 64.1 ± 8.5%, 46.2 ± 6.9%, and 47.3 ± 5.1, respectively (Fig. 3; Table 3).

The clinical characteristics of patients with and without recovery were shown in Table 3. There were no significant differences in baseline characteristics and clinical parameters in patients with AIC between those who recovered or not. By univariate analysis, patients who recovered had lower LVEF, received more HF medications (Table 3). Multivariate analysis confirmed standard HF medications (OR 9.39; 95% CI 2.27–52.9, $P=0.0014$) as an independent predictor of recovery (Table 4). Spontaneous recovery of LV systolic dysfunction without HF medications was observed in some

Table 2 Multivariate logistic model for anthracycline-induced cardiotoxicity

Variable	OR	CI	*P* value
Age	1.01	0.99–1.04	0.25
Female	1.49	0.71–3.13	0.29
Cardiac comorbidities	6.00	2.27–15.84	0.00044
Left chest radiation therapy	1.11	0.49–2.55	0.80
Cumulative anthracycline dose	1.00	1.00–1.01	0.15
Baseline LVEF	1.09	1.04–1.14	0.00034

OR odds ratio, *CI* per 1 unit increase or decrease of continuous variables, *LVEF* left ventricular ejection fraction

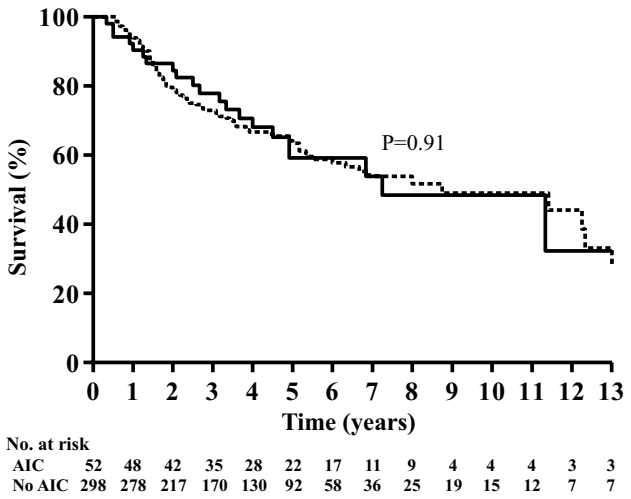

Fig. 2 Kaplan–Meier survival curve of patients with (solid line) or without (dashed line) the development of anthracycline-induced cardiotoxicity (AIC) after first anthracycline therapy

patients. There were no significant differences in baseline characteristics and clinical parameters in patients who recovered with or without HF medications. Patients with spontaneous recovery had smaller LV and higher LVEF. The changes of LVEF between at AIC and final follow-up time in patients who received HF medications was higher than those who did not (18.8 ± 13.4% vs 6.9 ± 10.4%, $P < 0.0015$). During the follow-up, the mortality tended to be lower in patients with AIC who recovered than those who did not (39.9% vs 51.3% at 5 years, Fig. 4), which, however, did not reach statistical significance.

In patients with recovery, 23 (69.7%) received HF medications (Table 3) and 12 out of 23 (52.2%) received them within 3 months after the last anthracycline. On the other hand, in patients without recovery, 4 (25.0%) received HF medications, but all received them later than 12 months ($P = 0.0052$, Fig. 5), suggesting early initiation of standard medical treatment for HF may lead to LV functional recovery in AIC.

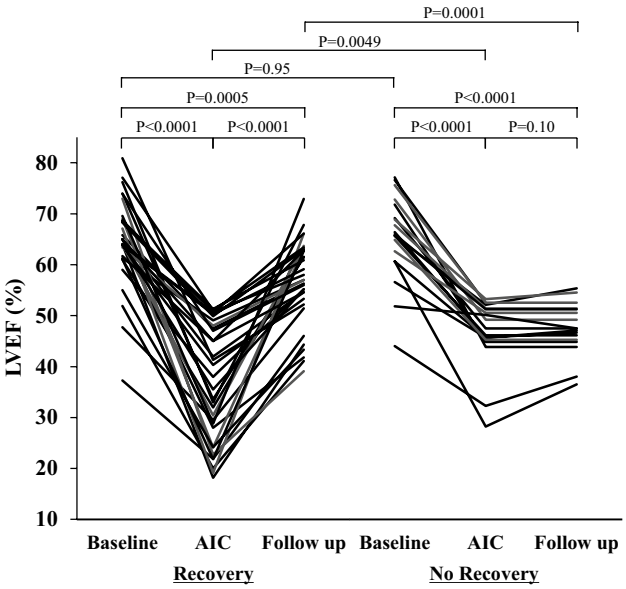

Fig. 3 Time-dependent changes of left ventricular ejection fraction (LVEF) at baseline, AIC, and follow-up for individual patients with anthracycline-induced cardiotoxicity (AIC) who recovered or not

Discussion

The present study represents a comprehensive appraisal of clinical evidence on the incidence and predictors of patients with AIC. The major findings of the present study are as follows; first, AIC occurred in 14.9% of cancer patients who were exposed to anthracycline at a median of 6 months after the commencement of anthracycline therapy. Second, cardiac comorbidities including ischemic heart disease, valvular heart disease, arrhythmia, and cardiomyopathy, cumulative anthracycline dose, and lower LVEF at baseline are predictors of AIC development. Finally, an early introduction of standard HF medications may lead to the recovery of AIC.

Anthracyclines are the most widely used chemotherapeutic agents with proven efficacy; however, their clinical benefit is limited by the complication of AIC. Although dose-dependent LV systolic dysfunction is the most common feature encountered at AIC, it varies from asymptomatic LV dysfunction to fatal HF. The incidence of AIC is relatively frequent and our present study revealed that clinically overt AIC developed in 6.6% of patients, which is consistent with a recent meta-analysis showing that clinically overt AIC occurred in 6% [13]. On the other hand, our data on asymptomatic LV dysfunction occurring in 8.3% of patients was less than that of the meta-analysis showing subclinical AIC occurred in 18% [13]. It is conceivable that more patients may experience asymptomatic LV dysfunction and the overall incidence of AIC can be underestimated. These findings imply that cardiac surveillance based only on symptoms might miss

Table 3 Demographic, clinical, and echocardiographic characteristics of the patients with and without recovery from LV systolic dysfunction

Characteristics	Total $N=49$	Recovery $N=33$	No recovery $N=16$	P value
Demographics				
Age at anthracycline treatment year	48 ± 16	50 ± 16	44 ± 16	0.18
Female	27 (55.1)	20 (60.6)	7 (43.8)	0.36
Body surface area, m^2	1.62 ± 0.17	1.61 ± 0.16	1.63 ± 0.19	0.60
Cardiovascular risk factors				
Hypertension	6 (12.2)	6 (18.2)	0 (0)	0.16
Diabetes mellitus	4 (8.2)	3 (9.1)	1 (6.3)	> 0.99
Hypercholesterolemia	4 (8.2)	2 (6.1)	2 (12.5)	0.59
Current or past smoker	22 (44.9)	14 (42.4)	8 (50.0)	0.76
Cardiac disease	12 (24.5)	9 (27.3)	3 (18.8)	0.73
Oncological disease				0.25
Lymphoma	23 (46.9)	14 (42.4)	9 (56.3)	
Leukemia	18 (36.7)	13 (39.4)	5 (31.3)	
Sarcoma	5 (10.2)	4 (12.1)	1 (6.3)	
Breast	2 (4.1)	2 (6.1)	0 (0)	
Others	1 (2.0)	0 (0)	1 (6.3)	
Left chest radiation therapy	19 (38.8)	10 (30.3)	9 (56.3)	0.12
Anthracycline dose				
Doxorubicin	25 (51.0)	16 (48.5)	9 (56.3)	0.76
Idarubicin	3 (6.1)	2 (6.1)	1 (6.3)	> 0.99
Pirarubicin	3 (6.1)	2 (6.1)	1 (6.3)	> 0.99
Daunorubicin	2 (4.1)	2 (6.1)	0 (0)	> 0.99
Epirubicin	1 (2.0)	1 (3.0)	0 (0)	> 0.99
Doxorubicin + idarubicin	1 (2.0)	1 (3.0)	0 (0)	> 0.99
Doxorubicin + pirarubicin	1 (2.0)	0 (0)	1 (6.3)	0.33
Doxorubicin + daunorubicin + mitoxantrone	2 (4.1)	0 (0)	2 (12.3)	0.10
Idarubicin + pirarubicin + mitoxantrone	1 (2.0)	1 (3.0)	0 (0)	> 0.99
Idarubicin + daunorubicin	2 (4.1)	2 (6.1)	0 (0)	> 0.99
Idarubicin + daunorubicin + mitoxantrone	4 (8.2)	2 (6.1)	2 (12.3)	0.59
Daunorubicin + mitoxantrone	4 (8.2)	4 (12.1)	0 (0)	0.29
Cumulative doxorubicin equivalent dose, mg/m^2	294 ± 131	275 ± 126	335 ± 138	0.14
Concomitant chemotherapy				
Alkylating agent	40 (81.6)	27 (81.8)	13 (81.3)	> 0.99
Antimetabolites	31 (63.2)	19 (57.6)	12 (75.0)	0.35
Microtubule-targeting agent	32 (65.3)	20 (60.6)	12 (75.0)	0.36
Topoisomerase inhibitor	16 (32.7)	8 (24.2)	8 (50.0)	0.11
Platinating agent	15 (30.6)	8 (24.2)	7 (43.8)	0.20
Molecular-targeted drug	22 (44.9)	14 (42.4)	8 (50.0)	0.76
Antitumor antibiotics	8 (16.3)	5 (15.2)	3 (18.8)	> 0.99
Hormone drug	30 (61.2)	18 (54.5)	12 (75.0)	0.22
Others	5 (10.2)	4 (12.1)	1 (6.3)	> 0.99
Medication for pre-existing disease				
ACE inhibitor or ARB	4 (8.2)	3 (9.1)	1 (6.3)	> 0.99
β-Blocker	4 (8.2)	4 (12.1)	0 (0)	0.29
Statin	3 (6.1)	2 (6.1)	1 (5.3)	> 0.99
Time to cardiotoxicity, month	6 (4–26)	6 (3–18)	9 (5–27)	0.24
NYHA functional class at AIC				0.18
I	27 (55.1)	15 (45.5)	12 (75.0)	
II	5 (10.2)	3 (9.1)	2 (12.5)	
III	9 (18.4)	8 (24.2)	1 (6.3)	

Table 3 (continued)

Characteristics	Total $N=49$	Recovery $N=33$	No recovery $N=16$	P value
IV	8 (16.3)	7 (21.2)	1 (6.3)	
Echocardiographic parameters at baseline				
LVDd, mm	48.5 ± 6.2	48.6 ± 6.9	48.3 ± 4.2	0.91
LVDs, mm	31.6 ± 5.3	31.5 ± 7.3	31.6 ± 5.3	0.97
LAD, mm	36.2 ± 10.9	37.8 ± 10.9	32.6 ± 10.4	0.21
LVEF, %	64.2 ± 9.4	64.3 ± 9.8	64.0 ± 9.0	0.95
LVEDVI, mL/m^2	69.7 ± 18.6	70.4 ± 21.5	68.2 ± 9.5	0.76
LVESVI, mL/m^2	25.9 ± 13.3	26.4 ± 15.3	24.8 ± 7.8	0.76
IVS, mm	8.2 ± 1.2	8.4 ± 1.2	7.6 ± 1.3	0.08
PW, mm	8.3 ± 1.0	8.4 ± 1.1	8.1 ± 0.9	0.47
E, cm/s	74.4 ± 24.4	71.7 ± 21.9	80.1 ± 26.7	0.38
E/A	1.2 ± 0.4	1.1 ± 0.4	1.4 ± 0.4	0.068
DT, ms	167.6 ± 35.0	174.5 ± 34.4	153.7 ± 33.7	0.13
Septal *e′*, cm/s	8.5 ± 2.3	8.2 ± 2.3	9.4 ± 2.3	0.17
E/e′	9.6 ± 5.1	9.7 ± 5.1	9.3 ± 5.5	0.84
s′	8.0 ± 1.7	8.1 ± 1.6	8.0 ± 2.1	0.89
IVC, mm	13.7 ± 4.5	13.0 ± 4.4	15.3 ± 4.5	0.17
Echocardiographic parameters at AIC				
LVDd, mm	49.4 ± 6.6	49.9 ± 6.8	48.5 ± 6.5	0.49
LVDs, mm	37.5 ± 6.5	38.7 ± 6.6	35.8 ± 5.3	0.13
LAD, mm	36.1 ± 9.5	36.6 ± 9.8	34.3 ± 8.6	0.44
LAVI, mL/m^2	42.8 ± 21.2	44.1 ± 22.9	36.9 ± 17.1	0.47
LVEF, %	46.1 ± 11.3	42.2 ± 11.2	51.2 ± 5.1	0.0016
LVEDVI, mL/m^2	74.3 ± 21.8	76.2 ± 21.5	70.5 ± 22.6	0.42
LVESVI, mL/m^2	41.1 ± 17.7	44.4 ± 19.1	34.3 ± 12.3	0.068
IVS, mm	8.6 ± 1.4	8.7 ± 1.5	8.4 ± 1.3	0.58
PW, mm	8.5 ± 1.3	8.6 ± 1.3	8.4 ± 1.2	0.76
E, cm/s	68.6 ± 29.8	70.6 ± 33.2	60.9 ± 15.8	0.28
E/A	1.2 ± 0.7	1.2 ± 0.8	1.1 ± 0.5	0.84
DT, ms	163.7 ± 63.9	155.5 ± 61.6	181.3 ± 67.7	0.24
Septal *e′*, cm/s	6.4 ± 2.2	6.0 ± 2.2	7.0 ± 2.3	0.19
E/e′	10.8 ± 5.1	11.2 ± 5.6	9.7 ± 4.1	0.39
s′	6.6 ± 1.3	6.4 ± 1.4	7.1 ± 1.0	0.12
IVC, mm	13.3 ± 4.3	13.3 ± 4.1	12.7 ± 4.6	0.68
Lowest LVEF, %	39.9 ± 11.2	36.8 ± 11.6	46.2 ± 6.9	0.0049
Current HF medication				
ACE inhibitor or ARB	24 (49.0)	20 (60.6)	4 (25.0)	0.032
β-Blocker	23 (46.9)	20 (60.6)	3 (18.8)	0.0073
ACE inhibitor or ARB or β-blocker	27 (55.1)	23 (69.7)	4 (25.0)	0.0054
Digitalis	3 (6.1)	2 (6.1)	1 (6.3)	> 0.99
Loop diuretics	10 (20.4)	9 (27.3)	1 (6.3)	0.13
Aldosterone antagonist	4 (8.2)	4 (12.1)	0 (0)	0.29

Data are presented as number (%) of patients, median (quartiles 1–3)

LVDd left ventricular diastolic diameter, *LVDs* left ventricular systolic diameter, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction, *LVEDVI* left ventricular end-diastolic volume index, *LVESVI* left ventricular end-systolic volume index, *DT* deceleration time, *ACE* angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker

Table 4 Multivariate logistic model for recovery from LV systolic dysfunction

Variable	OR	CI	*P* value
Age	1.03	0.98–1.08	0.19
Cardiac disease	0.52	0.06–4.16	0.53
Cumulative anthracycline dose	0.99	0.99–1.00	0.17
HF medications	9.39	2.27–52.9	0.0014

OR odds ratio, *CI* per 1 unit increase or decrease of continuous variables, *HF* heart failure

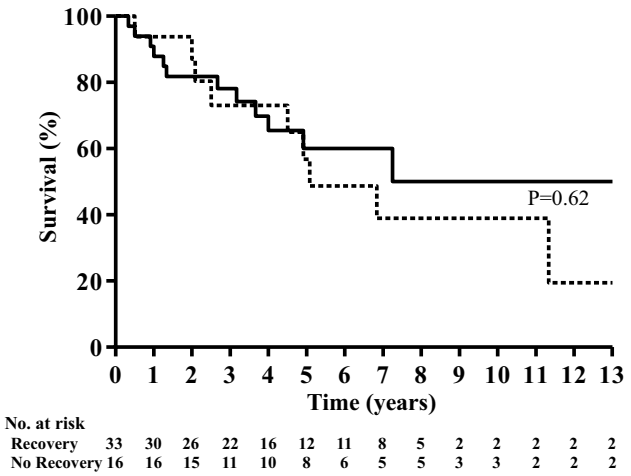

Fig. 4 Kaplan–Meier survival curve of patients who recovered (solid line) or did not recover (dashed line) from anthracycline-induced cardiotoxicity (AIC)

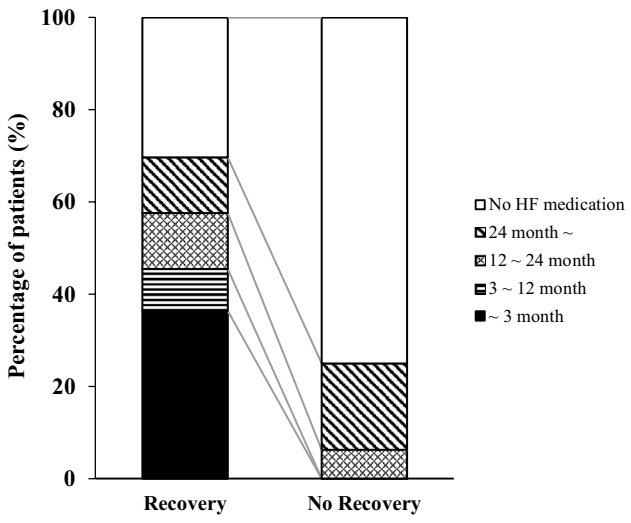

Fig. 5 Prevalence of intervals from last anthracycline exposure to the initiation of HF medications according to LV function recovery

the occurrence of AIC and underscore the importance of periodical cardiovascular assessment using echocardiography or multimodality imaging. In the present study, AIC occurred relatively early after the initiation of the anthracycline chemotherapy at a median of 6 months and 84.6% of AIC developed during the first year after completion of anthracycline chemotherapy, which was consistent with the recent study [10].

In our study, cardiac comorbidities and lower baseline LVEF are the strongest predictors of developing AIC, which were consistent with previous reports [14, 15]. Pre-existing cardiovascular diseases and LV dysfunction are major impediments to anthracycline use. In a study of patients with hematological malignancy, only 58% of patients with a history of HF received anthracycline-based chemotherapy compared with 70.8% of those without HF [14]. Previously, anthracycline use was not recommended in patients with LVEF < 30% [16]. Recent retrospective studies have questioned the utility of routine baseline LVEF measurement [17, 18], because this procedure did not affect the treatment decision. However, the value of baseline LVEF remained a significant predictor of AIC after adjustment for the cardiac comorbidities and clinical variables. Therefore, all patients to receive anthracyclines should undergo baseline echocardiogram to detect indolent LV dysfunction and obviate further cardiac damage [19–21]. Cardiovascular risk factors have been reported to be associated with the development of AIC [14]. However, the present study could not demonstrate the association between baseline cardiovascular risk factors and the development of AIC, which might be due to the paucity of patients with these risk factors in our study population.

Total cumulative anthracycline dose has been consistently reported as a strong predictor of AIC [13] and our results have also confirmed these findings. Prospective studies found that anthracycline-induced LV dysfunction occurred in 16.2%, 32.4%, 37.9%, and 53.9% of patients who received cumulative anthracycline doses of 300, 400, 450, 500 mg/m^2, respectively [22]. Recent guidelines recommend limiting the maximal dose of anthracycline lower than 450–550 mg/m^2 [23]. However, inter-individual variability exists in the maximal cumulative anthracycline dose tolerated, and it has been apparent from several reports that AIC could occur evenly in lower doses of anthracycline [24]. This phenomenon was collaborated by our observation that AIC develops at 14.9% of patients at the mean dose of 300 mg/m^2. The dose of anthracycline used in our study was significantly lower than the published data [10, 25, 26] and the least dose to develop AIC was 74 mg/m^2, which underscores the concept that a universally safe dose of the anthracycline to avert AIC does not exist. On the other hand, some patients could tolerate 600 mg/m^2 without evidence of carditoxicity and the threshold to develop AIC is determined not only by the anthracycline dose but also by the patient characteristics [5].

The clinical manifestation of AIC is traditionally considered to be refractory to old standard HF medications including only digoxin and diuretic [4] and LV dysfunction is less likely to recover compared with other forms of cardiomyopathy [27, 28]. LV dysfunction caused by AIC prompted the use of current standard HF medications including renin–angiotensin inhibitors and β-blockers, but there are few formal guidelines regarding the treatment and management of AIC. In our study, 42.9% of patients who developed AIC were treated with a combination of renin–angiotensin inhibitors and β-blockers and 12.2% were treated with renin–angiotensin inhibitors or β-blockers. Recent randomized control trials and meta-analyses show that these standard HF medications hold promise in the primary and secondary prevention of AIC [29–32]. Consistent with these studies, the present study demonstrated that HF medication was the only predictor of LVEF recovery. One of the critical factors in LVEF recovery from AIC is the early initiation of standard HF medication after completion of anthracycline treatment [9]. Notably, 81.5% of HF medication was initiated within 2 months after AIC development and 100% of these patients experienced cardiac recovery in our study. Despite the introduction of HF therapy, AIC is resistant to therapy if diagnosed late in its course [10, 33], highlighting the importance of early detection and timely intervention. Both renin–angiotensin inhibitors and β-blockers have antioxidant properties against anthracycline, which may be attributable to the interruption of a vicious cycle associated with HF [34, 35]. In support of this hypothesis, the recent clinical trial showed that HF medication did not reduce the increase in circulating troponin levels [29]. Although HF medication is associated with LVEF recovery, the mean LVEF of 56.9% after recovery remained significantly lower than that of baseline LVEF 64.3%, suggesting a certain level of irreversible anthracyline-induced cardiac damage or remodeling inflicted. The natural history of AIC has not been clearly elucidated, while spontaneous recovery of LV systolic dysfunction has been described [36, 37]. In the present study, LVEF recovery without HF medications was observed in some patients with less severe LV dysfunction. The mechanism for spontaneous recovery is not well-characterized, so identification of clinical parameters predictive of spontaneous recovery would be of great importance for the patient stratification and early referral to HF management. Although the functional mechanisms of renin–angiotensin inhibitors and β-blockers can be different for the prevention and treatment against AIC [29], the appropriate choice of HF medications and the best therapeutic strategies remain to be clarified. One of the challenging manifestation of AIC is the asymptomatic cardiac dysfunction and the optimal timing of HF mediations is not determined. What is more, patients receiving chemotherapy are vulnerable to hypovolemia due to side effects of chemotherapy and to develop hypotension by HF medications. Given the lack of conclusive evidence-based large clinical trials, initiation of standard HF medication is recommended in patients who develop LV dysfunction or at high risk of AIC.

Study limitations

Our study was limited by the retrospective nature of the available data at a single institution. Many patients without echocardiograms before chemotherapy could be included in this study. The timing of echocardiograms before and after chemotherapy was not uniform in each patient. The global and regional myocardial deformation parameters, in particular global longitudinal strain (GLS), which can be more sensitive to detect subclinical LV dysfunction than LVEF and can be useful for prediction of developing AIC [11, 38] were not available in this study. Consequently, the incidences of AIC and cardiac recovery were likely underestimated or overestimated.

Conclusions

This study showed that AIC is a relatively frequent complication in cancer patients, occurring mostly in the first year after completion of chemotherapy. Early detection of AIC and prompt treatment by standard medical treatment for HF may allow for recovery. These findings indicate that cardiologists and oncologists need to collaborate to improve the care of patients with AIC by maximizing the benefits of oncological outcome while reducing cardiovascular risks.

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Compliance with ethical standards

Conflict of interest Dr. Tsutsui has received the research grant from Actelion, Daichii-Sankyo, and Astellas, and lecture fees from Astellas, Otsuka, Takeda, Daichii-Sankyo, Mitsubishi Tanabe, Boehringer Ingelheim, Novartis, Bayer, and Bristol-Myers Squibb.

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