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Original article

Effect of standard low-dose anthracycline chemotherapy on late congestive heart failure in breast cancer survivors aged between 50 and 59 at diagnosis: A nationwide study

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ABSTRACT

Objectives: Although chemotherapy-induced congestive heart failure (CHF) is a well-known adverse event in cancer survivors, the long-term risk of standard low-dose anthracycline has not yet been reported. This study aimed to investigate the long-term effects of standard anthracycline on late CHF in breast cancer survivors.

Materials and methods: A nationwide retrospective cohort study was conducted using the national insurance claims data for nearly 98% of Korean citizens. Between Jan 2010 and Dec 2015, a total of 56,338 newly diagnosed female breast cancer survivors were included.

Results: The total number of person-years was 199,648 and the incidence rate of late CHF was 3.57 per 1000 person-years. In multivariate analysis according to the subject's age at diagnosis, only in the 50–59 age group, anthracycline-based [hazard ratio (HR) 1.765, 95% confidence interval (CI) 1.206–2.583] and taxane plus anthracycline-based regimens (HR 1.816, 95% CI 1.192–2.768) significantly increased the risk of late CHF. In the 50–59 age group, standard low-dose anthracycline significantly increased the risk of late CHF (HR 1.627, 95% CI 1.080–2.451) in Cox proportional hazard regression models. In competing risk model with recurrence and in-hospital death as competing risks, standard low-dose anthracycline was a significant risk factor for late CHF [subdistribution hazard ratio (SHR) 1.553, 95% CI 1.029–2.340].

Conclusion: This nationwide study showed that standard chemotherapy with low-dose anthracycline is a risk factor for late-onset CHF in breast cancer survivors who were in their 50 s at breast cancer diagnosis. Long-term monitoring of late CHF should be considered in these younger breast cancer survivors.

1. Introduction

Chemotherapy-induced congestive heart failure (CHF) is one of the most important adverse effects in cancer survivors [1,2]. Although high-dose anthracycline is a well-known risk factor for CHF, international guidelines do not recommend surveillance of CHF in patients treated with low-dose standard anthracycline alone because of low prevalence [3,4]. According to American Society of Clinical Oncology (ASCO) guidelines, no surveillance and monitoring is recommended in cancer patients treated with lower-dose anthracycline (e.g., doxorubicin, 250 mg/m^2; epirubicin, 600 mg/m^2) alone, if they have no additional risk factors.

However, previous studies have some limitations. They mainly focused on high-dose anthracycline, which is no longer used as the

Abbreviations: CHF, congestive heart failure; HR, hazard ratio; CI, confidence interval; SHR, subdistribution hazard ratio; ASCO, American Society of Clinical Oncology; HIRA, Health Insurance Review and Assessment Service; ICD-10, 10th revision of the International Classification of Diseases; CCI, Charlson Comorbidity Index; HT, hypertension; DM, diabetes mellitus; AC, cyclophosphamide plus anthracycline; FAC, fluorouracil plus anthracycline plus cyclophosphamide; AT, anthracycline plus taxane; ACT, anthracycline plus cyclophosphamide plus taxane; TC, taxane plus cyclophosphamide; TCab, taxane plus carboplatin; CMF, cyclophosphamide plus methotrexate plus fluorouracil.

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standard adjuvant chemotherapy [5,6]. Some studies were limited to early-onset CHF [5,7], and others were restricted to adolescent or old cancer survivors [6,8,9]. The lack of comprehensiveness among existing studies lead to a controversy regarding long-term monitoring for CHF. The National Comprehensive Cancer Network and ASCO guidelines do not recommend long-term screening beyond 1 year after finishing anthracycline or trastuzumab therapy [3,4]. However, the European Society for Medical Oncology have suggested long-term monitoring for CHF in cancer survivors [10].

Therefore, we conducted a large nationwide cohort study of 56,338 breast cancer survivors using data from the Health Insurance Review and Assessment Service (HIRA), which consists of data from nearly 98% of Korean citizens [11]. This study aimed to investigate the long-term effects of standard anthracycline on late CHF in breast cancer survivors.

2. Material and methods

2.1. Data source and extraction

The HIRA archives claim data including general information, diagnoses based on the 10th revision of the International Classification of Diseases (ICD-10), and healthcare services such as prescriptions, procedures, and treatments [11]. From Jan 2010 to Dec 2015, 203,956 patients tagged with codes C50 (invasive breast cancer) and V193, which is indicative of cancer patients for reimbursement, were extracted [12]. Among them, 87,237 patients already tagged with code C50 between Jan 2008 and Dec 2009 were excluded to eliminate previous cases (Supplementary Fig. S1). A total of 116,719 newly diagnosed breast cancer survivors were identified. We excluded 861 male patients, 6535 patients previously diagnosed with ductal carcinoma in situ, 15,297 metastatic or recent (within 2 years after breast cancer diagnosis) recurrent cases, 17,676 patients who did not undergo breast cancer surgeries, 16,226 patients with a previous or recent claim with another cancer code (code C), 3336 patients with a previous or recent (within 2 years following breast cancer diagnosis) history of CHF and 450 patients who had no follow-up after 2 years following breast cancer diagnosis.

2.2. Variables and operational definitions

Basic information and the Charlson Comorbidity Index (CCI) were evaluated [13]. The CCI is used to classify comorbid conditions in longitudinal studies and includes 19 medical conditions such as cardiovascular disease, liver disease, and pulmonary disease. Previous history of hypertension (HT), diabetes mellitus (DM), and dyslipidemia was evaluated based on the ICD-10 codes [HT, I10-13, 15, 16; DM, E10-14; and dyslipidemia, E78] and prescribed medications [14]. We defined the treatment groups based on claims data within 1 year after the breast cancer diagnosis. Surgery, radiation, (neo)adjuvant chemotherapy, (neo)adjuvant endocrine therapy, and trastuzumab were reviewed [12]. Patients were allocated into endocrine therapy groups based on the initially prescribed endocrine medication.

CHF was defined as three or more claims with the ICD-10 codes of heart failure (heart failure, I50; hypertensive heart disease with heart failure, I110) [15,14]. Physicians can enter the ICD-10 codes just to rule out CHF. To tackle the problem, we excluded rule-out diagnoses of CHF and only included the ones with the definite diagnoses of CHF. Because rule-out diagnoses and definite diagnoses are stored separately into this billing system, rule-out diagnoses can be distinguished from definite diagnoses in the database. In-hospital mortality was included in the analysis because the HIRA only archives mortality information from hospitals. Recurrence or metastasis was defined as breast cancer diagnosis with metastatic codes, claims for second-line or more systemic treatments, or radiation at distant metastatic sites.

(Neo)adjuvant chemotherapy was categorized in three ways. Category 1 included none, anthracycline-based, taxane plus anthracycline-based, taxane-based, and other chemotherapy regimen. Category 2 was divided into none, cyclophosphamide plus anthracycline (AC), fluorouracil plus anthracycline plus cyclophosphamide (FAC), anthracycline plus taxane (AT), anthracycline plus cyclophosphamide plus taxane (ACT), taxane plus cyclophosphamide (TC), taxane plus carboplatin (TCab), and cyclophosphamide plus methotrexate plus fluorouracil (CMF). Category 3 was classified as no-chemotherapy and standard low-dose anthracycline groups. The standard low-dose anthracycline group was defined as patients treated with only four cycles of anthracycline during the entire study period because low-dose anthracycline is defined as doxorubicin less than 250 mg/m^2 or epirubicin less than 600 mg/m^2 in the international guidelines [4].

For landmark analysis, the index date was defined as the date 2 years after breast cancer diagnosis. Late-onset CHF was defined as CHF which developed after 2 years following breast cancer diagnosis [15].

2.3. Selection of high-risk age group for late CHF

To identify the high-risk age groups for late CHF, subjects were divided according to their age at diagnosis (<40, 40–49, 50–59, and ≥60). Cox proportional hazard regression analysis was performed for the entire population and the age subgroups, adjusted for (neo)adjuvant chemotherapy category 1, age at diagnosis, insurance (health insurance or medicare), CCI, previous DM, HT and dyslipidemia, radiation, trastuzumab, and endocrine therapy. The age group that was most influenced by (neo)adjuvant chemotherapy with regards to late CHF was selected as the main study population.

Statistical analysis

Descriptive statistics among the high-risk age groups for late CHF are summarized with absolute and relative frequencies. To assess the risk of late CHF according to the (neo)adjuvant chemotherapy regimen (category 2), Cox proportional hazards regression models were constructed. The models adjusted for age at diagnosis in Model 1, age at diagnosis, insurance and past medical history in Model 2, and age at diagnosis, insurance, past medical history, and adjuvant treatments in Model 3. We created a Fine and Gray competing risk regression model with recurrence and in-hospital death as competing events with adjustments for the covariates used in Cox Model 3 [16,17].

In the high-risk age group for late CHF, to investigate the long-term effects of standard low-dose anthracycline on late CHF, the group that received standard low-dose anthracycline was extracted and compared with patients who received no chemotherapy. A Kaplan–Meier analysis and log-rank test were used to assess the late CHF-free probability. We fit the Cox proportional hazards regression models with the same adjustments as above. The proportional hazards assumption using the scaled Schoenfeld residuals test was analyzed. Cumulative incidence function and competing risk regression model were created with recurrence and in-hospital death as competing risks. Sensitivity analysis was also performed, excluding subjects with a previous DM, HT, or dyslipidemia, which are known risk factors for heart diseases [18–20].

Statistical analyses were performed with SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) and R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). All *P* values reported are two-sided. $P < 0.05$ was considered to indicate statistical significance. This study was approved by the Institutional Review Board of Asan Medical Center (IRB no. 2019–0875).

3. Results

3.1. Basic characteristics

A total of 56,338 cases were included in this analysis (Supplementary Table S1). The mean follow-up period was 66.8 months and the total number of person-years was 199,648 (Supplementary Table S2). The incidence rate for late CHF was 3.57 per 1000 person-years.

3.2. Selection of high-risk age group

In multivariate analyses among the total population, the anthracycline-based [hazard ratio (HR) 1.245, 95% confidence interval (CI) 1.024–1.514] and taxane plus anthracycline-based regimen (HR 1.247, 95% CI 0.985–1.578) showed increased risks of late CHF in the fully adjusted Cox proportional hazards model (Supplementary Table S2). In subgroup analysis based on age at diagnosis, the anthracycline-based (HR 1.765, 95% CI 1.206–2.583) and taxane plus anthracycline-based (HR 1.816, 95% CI 1.192–2.768) regimens significantly increased the risks of late CHF only in the 50–59 age group, which we selected as the main study subjects. Table 1 presents the basic characteristics of the 50–59 age group according to (neo)adjuvant chemotherapy regimens.

3.3. Late CHF in breast cancer survivors aged between 50 and 59 at diagnosis

In the 50–59 age group, the AC, FAC, and ACT regimens were associated with an increased risk of late CHF in all adjusted models (Supplementary Tables S3–S4). After adjustment for age, insurance, past medical history, and other adjuvant treatments, the associations were statistically significant (AC, HR 1.672, 95% CI 1.095–2.555; FAC, HR 2.006, 95% CI 1.260–3.196; ACT, HR 1.922, 95% CI 1.260–2.932) and they remained significant [AC, subdistribution hazard ratio (SHR) 1.720, CI 1.110–2.670; FAC, SHR 1.950, CI 1.190–3.190; ACT, SHR 1.700, CI 1.100–2.630] after competing risk analyses (Supplementary Table S5).

3.4. Association between standard low-dose anthracycline and late CHF in breast cancer survivors aged between 50 and 59 at diagnosis

In the 50–59 age group, we selected 5643 patients treated with standard low-dose anthracycline during the study period. We chose 6220 subjects who never received chemotherapy during the study period as a control (Table 2). Kaplan–Meier analysis showed that the CHF-free probability was significantly lower (Log-rank test, $P = 0.008$) in the standard low-dose anthracycline group than in the no-chemotherapy group (Fig. 1). The risk of late CHF was significantly associated with standard low-dose anthracycline use (in Model 3, HR 1.627, CI 1.080–2.451) in all multivariate analyses (Table 3). After competing risk analyses, the results persisted (Gray's test, $P = 0.027$; SHR 1.553, CI 1.029–2.340, Supplementary Fig. S2 and Supplementary Table S6). The scaled Schoenfeld residuals test showed no evidence that the proportional hazards assumption had been violated ($P = 0.266$, Supplementary Fig. S3). Lastly, in sensitivity analysis, although we excluded subjects with a previous history of DM, HT, or dyslipidemia, the results were essentially unchanged (Supplementary Table S7).

4. Discussion

This nationwide cohort study showed that breast cancer survivors aged between 50 and 59 at diagnosis were at a high risk for late CHF. In this age group, standard low-dose anthracycline use significantly increased the risk of late CHF. Trastuzumab and adjuvant chemotherapy without anthracycline were not related to the risk of late CHF.

This study provides a new perspective regarding the effect of standard low-dose anthracycline on the development of late CHF. In this study, standard low-dose anthracycline increased the risk of late CHF in relatively young survivors aged 50–59 years at breast cancer diagnosis. Our results provide an explanation for the lack of consensus concerning the long-term risk of CHF after anthracycline use [4,10]. In terms of the late-onset cardiotoxicity, weak risk

Table 1
Basic characteristics of breast cancer survivors aged 50–59 years at diagnosis according to (neo)adjuvant chemotherapy regimens.

Parameters	None		Anthracycline-based		Taxane + Anthracycline-based		Taxane-based		Chemotherapy, others	
	N (%)		*N* (%)		*N* (%)		*N* (%)		*N* (%)	
Total	6247		5655		3474		348		1261	
Age at diagnosis (years, Mean ± SD)	53.8 ± 2.9		53.8 ± 2.8		53.8 ± 2.8		54.2 ± 2.8		53.9 ± 2.8	
Insurance										
Health insurance	6138	(98.3)	5578	(98.6)	3409	(98.1)	337	(96.8)	1229	(97.5)
Medicare	109	(1.7)	77	(1.4)	65	(1.9)	11	(3.2)	32	(2.5)
CCI (Mean ± SD)	2.1 ± 1.7		2.0 ± 1.7		1.9 ± 1.7		2.2 ± 1.8		2.2 ± 1.8	
previous diabetes mellitus	435	(7.0)	423	(7.5)	287	(8.3)	28	(8.0)	108	(8.6)
previous hypertension	1580	(25.3)	1474	(26.1)	931	(0.3)	78	(22.4)	355	(28.2)
previous dyslipidemia	1965	(31.5)	1726	(30.5)	1032	(0.3)	109	(31.3)	396	(31.4)
(Neo)adjuvant endocrine therapy										
None	1513	(24.2)	2169	(38.4)	1112	(32.0)	133	(38.2)	348	(27.6)
Tamoxifen	1855	(29.7)	1138	(20.1)	690	(19.9)	74	(21.3)	267	(21.2)
AI	2879	(46.1)	2348	(41.5)	1672	(48.1)	141	(40.5)	646	(51.2)
Radiation	4189	(67.1)	4167	(73.7)	2734	(78.7)	261	(75.0)	919	(72.9)
Trastuzumab	95	(1.5)	1518	(26.8)	993	(28.6)	125	(35.9)	165	(13.1)
Incidence										
Late CHF diagnosis	46	(0.7)	78	(1.4)	47	(1.4)	1	(0.3)	18	(1.4)
In-hospital mortality	55	(0.9)	89	(1.6)	102	(2.9)	1	(0.3)	24	(1.9)
Duration after cohort entry (mean ± SD, month)	64.9 ± 20.4		69.7 ± 19.0		64.1 ± 19.9		43.2 ± 8.0		74.1 ± 19.7	

CCI, Charlson Comorbidity Index; CHF, congestive heart failure; SD, standard deviation.

Table 2
Basic characteristics of no-chemotherapy and standard low-dose anthracycline subgroup among breast cancer survivors aged 50–59 years at diagnosis.

Parameters	No-chemotherapy		Low-dose anthracycline	
	N (%)		*N* (%)	
Total	6220		5643	
Age at diagnosis (years, Mean ± SD)	53.8 ± 2.9		53.8 ± 2.8	
Insurance				
Health insurance	6111	(98.2)	5559	(98.5)
Medicare	109	(1.8)	84	(1.5)
CCI (Mean ± SD)	2.1 ± 1.7		2.0 ± 1.7	
previous DM	432	(6.9)	453	(8.0)
previous HT	1571	(25.3)	1517	(26.9)
previous DYS	1961	(31.5)	1752	(31.0)
(Neo)adjuvant chemotherapeutic regimens				
None	6220	(100)	0	(0.0)
AC/EC	0	(0.0)	2966	(52.6)
ACT	0	(0.0)	2677	(47.4)
(Neo)adjuvant endocrine therapy				
None	1499	(24.1)	1835	(32.5)
Tamoxifen	1848	(29.7)	1188	(21.1)
AI	2873	(46.2)	2620	(46.4)
Radiation	4171	(67.1)	4325	(76.6)
Trastuzumab	95	(1.5)	1623	(28.8)
Incidence				
Late CHF diagnosis	45	(0.7)	67	(1.0)
In-hospital mortality	41	(0.7)	87	(1.5)
Duration after cohort entry (mean ± SD, month)	64.8 ± 20.4		64.0 ± 18.2	

factors (age in 50's) seemed to be important. In this study, old patients (60 years and above) who were treated with anthracycline did not show an increased risk of late CHF (Supplementary Table S2). However, weak risk factors such as low-dose anthracycline and age in 50's significantly increased the risk of late CHF. This suggests that long-term monitoring of late CHF taking into accounts various weak risk factors should be considered.

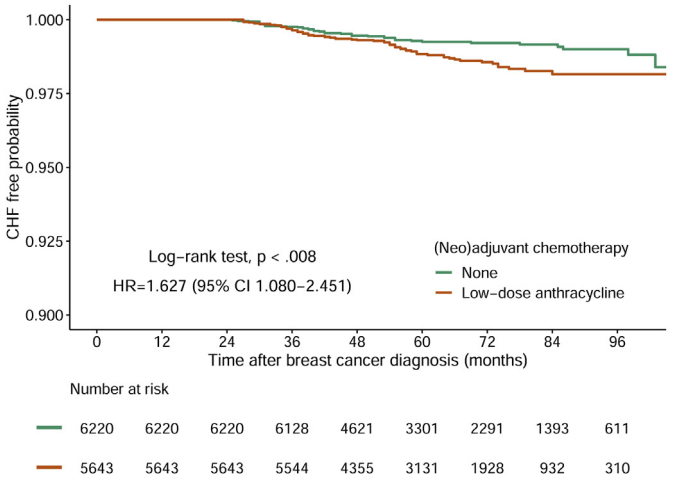

Fig. 1. Kaplan–Meier curve of late congestive heart failure between no-chemotherapy group and standard low-dose anthracycline subgroup among breast cancer survivors aged 50–59 years at diagnosis.

Several theories can be suggested to explain why only breast cancer survivors aged 50–59 years showed an increased risk of late CHF after standard anthracycline chemotherapy in this study. First, because older breast cancer patients aged 60 years and above are at a high risk for CHF, adjuvant anthracycline treatment can cause immediate or early-onset CHF. Second, in practice, clinicians are usually reluctant to administer full standard doses of chemotherapy to older patients, which may lead to reduced effects of anthracycline on CHF. In contrast, younger breast cancer patients aged 50–59 years are assumed to be at a lower risk for CHF and consequently, standard doses of anthracycline are usually administered. Lastly, the likelihood of developing late CHF can vary according to age. Interestingly, anthracycline-based regimens showed an increased trend in late CHF (HR 1.520, CI 0.937–2.467, $P = 0.090$) in breast cancer survivors aged between 40 and 49 (Supplementary Table S2).

Radiotherapy is a well-known risk factor for heart disease [21–23]. A previous population-based case-control study showed that radiotherapy for breast cancer increased the rate of ischemic

Table 3
Cox proportional hazards regression analysis of late CHF risk between no-chemotherapy and standard low-dose anthracycline subgroup among breast cancer survivors aged 50–59 years at diagnosis.

Regimen	Cases, *N*	Events, *N*	Person-years	Late CHF IR per 1000 person-years	Model 1[a]			Model 2[b]			Model 3[c]		
					HR (95% CI)		*P*	HR (95% CI)		*P*	HR (95% CI)		*P*
None	6220	45	21,085	2.13	1	(reference)		1	(reference)		1	(reference)	
Low-dose anthracycline	5643	67	18,679	3.59	1.664	(1.140–2.429)	0.008	1.640	(1.123–2.396)	0.011	1.627	(1.080–2.451)	0.020

IR, incidence rate; HR, hazard ratio; CI, confidence interval; CHF, congestive heart failure.
[a] Model 1: adjusted for age at diagnosis (continuous).
[b] Model 2: adjusted for age at diagnosis (continuous), insurance (health insurance or medicare), Charlson Comorbidity Index (continuous), previous hypertension, previous diabetes mellitus, previous dyslipidemia.
[c] Model 3: adjusted for the covariates used in Model 2, radiotherapy, trastuzumab, endocrine therapy (tamoxifen, none, aromatase inhibitor).

heart disease [21]. In our study, radiation therapy did not increase the rate of late CHF (SHR 0.805, CI 0.526–1.230). However, our results should be interpreted with caution. We excluded subjects with a previous or recent history of CHF, the mean follow-up period was shorter than that of previous studies, and the outcome variable was CHF in our study, not ischemic heart disease. Moreover, the HIRA data does not archive detailed information about radiation therapy, including sides of the treated breast (right or left), the radiation fields (e.g. internal mammary lymph node) and the radiation technique (e.g. intensity-modulated). Thus, the effect of radiotherapy cannot be confirmed from this study.

In previous studies, trastuzumab was not associated with late CHF in breast cancer patients because its effect on cardiac function is reversible [24,25]. Trastuzumab began to be covered by the national insurance from 2010 in South Korea and we were able to analyze its long-term effects on late CHF. In our study, trastuzumab did not increase the risk of late CHF in breast cancer survivors, similar to the results in previous studies.

Several limitations of our study should be noted. First, although we conducted survival analysis with in-hospital mortality, it should not be interpreted as overall survival. Because the HIRA collects data only from hospitals, the HIRA data does not have any mortality information from patients who died anywhere outside of hospital. Moreover, the HIRA does not have any data about cause of death. We were not able to analyze the cause-specific mortality in this study. Second, the HIRA does not archive information about stage, laboratory results, lifestyle factors such as diet, smoking, obesity, or physical activities, and details about radiation therapy. Third, although we developed algorithms which we used to define metastatic or recurred breast cancers, there remains a possibility that some recurrent or metastatic cases were included in the analysis. Fourth, because the claimed data did not have information about uninsured procedures or tests such as echocardiography after the completion of chemotherapy or trastuzumab, we were not able to analyze frequencies of echocardiography in this population. Fifth, although we used several approaches to enhance the accuracy of the diagnosis of CHF, the severity of congestive heart failure could not be estimated because the diagnoses were only based on diagnostic codes. Finally, the exact doses of anthracycline administered to subjects were not evaluated.

5. Conclusions

This nationwide cohort study showed that standard chemotherapy with low-dose anthracycline is a risk factor for late-onset CHF in breast cancer survivors who were in their 50 s at breast cancer diagnosis. Long-term monitoring of late CHF should be considered in these younger breast cancer survivors.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.07.006.

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