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ORIGINAL ARTICLE

Fibroblast growth factor-23 in HER2 positive breast cancer: its expression and correlation with adjuvant EC->D+T treatment induced cardiotoxicity risk

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Summary

Purpose: *The purpose of this study was to explore fibroblast growth factor-23 (FGF-23) expression and its predictive value on cardiotoxicity risk induced by adjuvant trastuzumab combined with chemotherapy in HER2 positive (HER2⁺) breast cancer patients.*

Methods: *Enrolled were 105 HER2⁺ breast cancer patients about to receive adjuvant epirubicin combined with cyclophosphamide followed by docetaxel and trastuzumab (EC->D+T) treatment after surgery. Their serum FGF-23 levels pre adjuvant therapy were determined by enzyme linked-immunosorbent assay (ELISA). Cardiotoxicity was monitored at 3 months (M), M6, M9, M12, and M15 after treatment.*

Results: *The mean FGF-23 level was 333.7±130.3 pg/ml, and it was correlated with increased rates of hypertension (p=0.014) and chronic kidney disease (CKD) (p=0.025), decreased LVEF (r=-0.250, p=0.010), elevated cardiac troponin I (cTnl) (r=0.395, p<0.001) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (r=0.367, p<0.001). Regarding cardiotoxicity rate, it was 0.0%, 0.0%, 1.9%, 11.4%, 17.1% and 19.0% at M0, M3, M6, M9, M12 and M15 respectively, which was stable at M0 and M3, while was obviously increased from M3 to M15. Compared with non-cardiotoxicity patients, FGF-23 level was higher in cardiotoxicity patients (410.1±165.2 vs. 315.7±114.6 pg/ml) (p=0.003), and it (p=0.021) was an independent risk factor predicting cardiotoxicity by multivariate logistic regression analysis, also had a good predictive value for cardiotoxicity risk (AUC: 0.664; 95%CI: 0.529-0.799) by receiver operating characteristic (ROC) curves.*

Conclusions: *FGF-23 is upregulated and correlates with hypertension, CKD and poor cardiac function. Importantly, it is an independent risk factor predicting adjuvant EC->D+T treatment induced cardiotoxicity in HER2⁺ breast cancer patients.*

Key words: *fibroblast growth factor-23, cardiotoxicity risk, human epidermal growth factor receptor-2, breast cancer, adjuvant EC->D+T treatment*

Introduction

Breast cancer is the second most common malignant tumor and also the fourth most common cancer-related cause of death globally, which caused 2,088,849 new cases (11.6% of all new cancer cases) and 626,679 cancer-related deaths (6.6% of all cancer- related deaths) around the word in 2018 [1]. As one of the most common molecular subtypes of breast cancer, human epidermal growth factor receptor-2 (HER2⁺) breast cancer (accounting on approximately 15-20% of all breast cancers) tends to be diagnosed in younger patients [2,3]. Currently, disease management of HER2⁺ breast cancer focuses on surgery with neoadjuvant or adjuvant treatment using a combination of HER2 targeted blocking agents (including trastuzumab, pertuzumab and neratinib etc.) and chemotherapy (such as epirubicin combined with cyclophosphamide followed by docetaxel (EC->D) regimen) [3,4].

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Despite the improvements on survival obtained in these HER2+ breast cancer patients, HER2 targeted blocking agents present obvious side effects of serious cardiotoxicity, which causes various cardiac adverse events (such as decreased ejection fraction, acute coronary artery syndrome, fatal arrhythmia and heart failure) [5]. Also, chemotherapy contributes to increased cardiotoxicity risk to some extent [6]. Thus, HER2 targeted blocking agents and chemotherapy induced cardiac adverse events have been issues of particular concern in HER2+ breast cancer patients.

Fibroblast growth factor-23 (FGF-23), a kind of 251-amino-acid protein involved in calcium–phosphate homoeostasis, is primarily secreted by osteocytes, which is a major regulator of vitamin D and phosphate homeostasis [7]. A previous animal study revealed that the direct myocardial delivery of FGF-23 induces the myocyte hypertrophy and left ventricular hypertrophy (LVH) *in vivo* [8]. In addition, FGF-23 also has an obvious relationship with high risk of cardiac adverse events in patients with several diseases (including chronic kidney disease (CKD) [9], gestational diabetes [10] and non-occlusive mesenteric ischemia (NOMI) [11]). However, little was known about the role of FGF-23 in breast cancer patients with high cardiotoxicity risk, such as those who receive HER2 targeted blocking agents and chemotherapy with anthracycline drugs.

In our research center and even in China, epirubicin combined with cyclophosphamide followed by docetaxel and trastuzumab (EC->D+T) is the most common adjuvant therapy for HER2+ breast cancer patients. Hence, this study aimed to explore the clinical implication of FGF-23 on cardiotoxicity risk in HER2+ breast cancer patients receiving adjuvant EC->D+T treatment.

Methods

Patients

Between January 2016 and December 2018, 105 HER2+ breast cancer patients about to receive adjuvant chemotherapy with EC->D+T regimen after surgery in our hospital were consecutively enrolled in this study. All patients met the following inclusion criteria: (i) histologically and clinically diagnosed breast cancer, with HER2+ tumor status which was confirmed by immunohistochemistry 3+ staining or 2+ staining plus fluorescence *in situ* hybridization positivity; (ii) age ≥18 years; (iii) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1; (iv) suitable for adjuvant chemotherapy with EC->D+T regimen, which was demonstrated by adequate renal function (serum creatinine clearance >60 ml/min), hepatic function (bilirubin <upper normal limit (UNL), alkaline phosphatase <5 UNL, aminotransferases <2.5 UNL), hematology (hemoglobin >10 g/dl, absolute neutrophil count $>1.5\times10^9$/L, platelets $>100\times10^9$/L), and cardiac function (left ventricular ejection fraction (LVEF) ≥55%); (v) wiling to comply with the scheduled follow-up. Patients with the following conditions were excluded: (i) contraindications to chemotherapy regimen; (ii) received neoadjuvant chemotherapy before surgery; (iii) serious cardiac illness, including history of congestive heart failure, acute myocardial infarction within 6 months, evidence of transmural infarction in echocardiography, evidence of high-risk uncontrolled arrhythmias, angina pectoris requiring antianginal medication, and clinically significant valvular heart disease; (iv) complicated with active infections, inflammatory diseases, or hematologic diseases; (v) history of cancers; (vi) pregnant women.

Ethics approval

The Ethics Committee of our hospital gave approval for conducting this study (12-69/603). All study procedure was fully conformed with the principles of the Declaration of Helsinki, and all patients signed the informed consents.

Baseline data collection

Demographics (age, body mass index (BMI), and smoke status), comorbidities (hypertension, hyperlipidemia, diabetes mellitus, hyperuricemia, and CKD) and ECOG PS of patients were documented after baseline screening. LVEF, cardiac troponin I (cTnI) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were recorded after baseline cardiac function assessment.

Peripheral blood (PB) collection and determination

PB of patients was sampled before initiation of adjuvant chemotherapy. After sampling, serum was separated from PB by centrifuging at 2000 × g for 15 min in a refrigerated centrifuge, then was stored at -70°C until following determination. The serum FGF-23 level was determined by enzyme linked-immunosorbent assay (ELISA) with the use of Human FGF-23 ELISA Kit (R&D Systems, Minneapolis, Minnesota, USA). ELISA was carried out according to the manufacturer's instructions. Standard curve was constructed using standards in the kit, and the absorbance was read at 450 nm. The concentration for unknown samples was calculated from the standard curve.

Adjuvant chemotherapy with EC->D+T regimen

All patients received EC->D+T adjuvant chemotherapy regimen, which was administered as follows: epirubicin (E) 100 mg/m^2 intravenously (IV) and cyclophosphamide (C) 600 mg/m^2 IV (EC) on day 1 every 21 days for 4 cycles followed by docetaxel (D) 100 mg/m^2 IV on day 1 every 21 days for 4 cycles. Trastuzumab (T) was weekly initiated concurrently with docetaxel, at first dose of 4 mg/kg IV and subsequent doses of 2 mg/kg IV. After completion of D treatment, trastuzumab was administered at dose of 6 mg/kg IV every 21 days to complete a year of T treatment.

Cardiotoxicity supervising

LVEF of patients was evaluated by ultrasound cardiogram for monitoring cardiotoxicity, which was performed every 3 months (at 3 months (M3), 6 months (M6), 9 months (M9), 12 months (M12), and 15 months (M15)) after initiation of adjuvant chemotherapy, and absolute change value of LVEF at each assessment was calculated. Cardiotoxicity was defined as one of the following situations: (i) an absolute decline of LVEF (ΔLVEF) at least 10 percentage points from baseline to a value <53% identified by echocardiogram, (ii) heart failure, (iii) acute coronary artery syndrome, or (iv) fatal arrhythmia [12-14].

Statistics

Statistical data processing and analyses were completed using SPSS 22.0 statistical software (IBM, Chicago, Illinois, USA), and figures were drawn using GraphPad Prism 8.01 (GraphPad Software Inc., San Diego, California, USA). Data were shown as mean with standard deviation (M±SD) or number with percentage (No. (%). FGF-23 level distribution was displayed using histogram, and comparison of FGF-23 between different subjects was determined by Student's t-test. Correlation between FGF-23 and other variables was analyzed by Spearman's rank correlation test. Receiver-operating characteristic (ROC) curve and the area under the ROC curve (AUC) were used to evaluate the performance of variables in the prediction of cardiotoxicity. Univariate and multivariate logistic regression were performed to analyze the factors associated with cardiotoxicity, and the forward stepwise (conditional) method was used to screen the independent factors in the multivariate logistic regression analysis. P value less than 0.05 was considered as statistically significant.

Results

Clinical characteristics

In 105 HER2+ breast cancer patients, the mean value of age and BMI was 51.8±7.1 years and 22.0±2.3 kg/m^2 respectively. Regarding comorbidities, there were 19 (18.1%), 13 (12.4%), 7 (6.7%), 16 (15.2%) and 8 (7.6%) patients with hypertension, hyperlipidemia, diabetes mellitus, hyperuricemia and CKD, respectively. Besides, 84 (80.0%) patients had ECOG 0 score, and 21 (20.0%) ECOG 1 score. Regarding cardiac function, the mean value of LVEF, cTnI and NT-proBNP was 68.0±3.8%, 41.2±33.8 pg/ml and 78.4±34.5 pg/ml, respectively. The detailed information about other clinical features are shown in Table 1.

FGF-23 level and its correlation with clinical features

FGF-23 expression was mainly distributed between 200 and 400 pg/ml (mean 333.7±130.3 pg/ml) (Figure 1). In addition, FGF-23 high level was correlated with hypertension (p=0.014) and CKD (p=0.025), while there was no difference in the correlation of FGF-23 with smoke (p=0.288), hyperlipidemia (p=0.090), diabetes mellitus (p=0.435), hyperuricemia (p=0.735) and ECOG PS (p=0.916) (Table 2). Furthermore, FGF-23 level was positively correlated with cTnI (r=0.395, p<0.001) and NT-proBNP (r=0.367, p<0.001), while it was negatively correlated with LVEF (r=-0.250, p=0.010).

Table 1. Clinical patient features

Items	*HER2+ breast cancer patients (n=105)*
Demographics	
Age (years), M±SD	51.8±7.1
BMI (kg/m^2), M±SD	22.0±2.3
Smoker, n (%)	18 (17.1)
Comorbidities	
Hypertension, n (%)	19 (18.1)
Hyperlipidemia, n (%)	13 (12.4)
Diabetes mellitus, n (%)	7 (6.7)
Hyperuricemia, n (%)	16 (15.2)
Chronic kidney disease, n (%)	8 (7.6)
ECOG PS, n (%)	
0	84 (80.0)
1	21 (20.0)
Cardiac function	
LVEF (%), M±SD	68.0±3.8
cTnI (pg/ml), M±SD	41.2±33.8
NT-proBNP (ng/ml), M±SD	78.4±34.5

HER2+: human epidermal receptor 2 positive; M±SD: mean ± standard deviation; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; LVEF: left ventricular ejection fraction; cTnI: cardiac troponin I; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

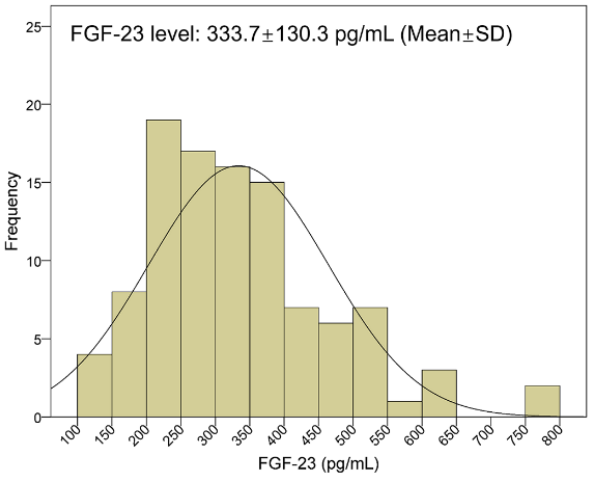

Figure 1. FGF-23 distribution in HER2+ breast cancer patients. FGF-23: fibroblast growth factor 23; HER2+: human epidermal receptor 2 positive; SD: standard deviation.

Meanwhile, there was no correlation of FGF-23 with age (r=0.148, p=0.131) and BMI (r=-0.012, p=0.902) (Table 3).

Accumulating cardiotoxicity rate

The accumulating cardiotoxicity rate was 0.0%, 0.0%, 1.9%, 11.4%, 17.1% and 19.0% at M0, M3, M6, M9, M12 and M15, respectively, and it was stable at M0 and M3, while it was obviously increased from M3 to M15 (Figure 2). Among the accumulating cardiotoxicity cases, there were 20 (19.0%) cases with accumulating ΔLVEF≥10% & LVEF<53%, 0 (0.0%) case with accumulating heart failure, 2 (1.9%) cases with accumulating acute coronary syndrome and 0 (0.0%) case with accumulating life-threatening arrhythmias.

Comparison of FGF-23 level between non-cardiotoxicity and cardiotoxicity patients

The mean value of FGF-23 level was 315.7±114.6 pg/ml in non-cardiotoxicity patients and 410.1±165.2 pg/ml in cardiotoxicity patients. Compared with non-cardiotoxicity patients, FGF-23 level was higher in cardiotoxicity patients (p=0.003) (Figure 3).

Factors associated with cardiotoxicity risk

Univariate logistic regression analysis revealed that FGF-23 (p=0.007), age (p=0.004), hypertension (p=0.035), cTnI (p=0.021) and NT-proBNP (p=0.042) were associated with increased risk of cardiotox-

Table 2. Correlation of FGF-23 with categorical variables of clinical feature

Items	*FGF-23 (pg/mL), M±SD*	*p value*
Smoker		0.288
Yes	312.2±80.5	
No	338.1±138.4	
Hypertension		0.014
Yes	339.9±138.9	
No	319.1±124.5	
Hyperlipidemia		0.090
Yes	391.0±164.3	
No	325.6±123.8	
Diabetes mellitus		0.435
Yes	371.1±118.8	
No	331.0±131.3	
Hyperuricemia		0.735
Yes	323.5±110.5	
No	335.5±134.1	
Chronic kidney disease		0.025
Yes	432.3±130.9	
No	325.6±127.6	
ECOG PS		0.916
1	336.4±147.8	
0	333.0±126.6	

FGF-23: fibroblast growth factor 23; M±SD: mean ± standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status.

Table 3. Correlation of FGF-23 with continuous variables of clinical feature

Items	*FGF-23*	
	r	*p value*
Age	0.148	0.131
BMI	-0.012	0.902
LVEF	-0.250	0.010
cTnI	0.395	<0.001
NT-proBNP	0.367	<0.001

FGF-23: fibroblast growth factor 23; BMI: body mass index; LVEF: left ventricular ejection fraction; cTnI: cardiac troponin I; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

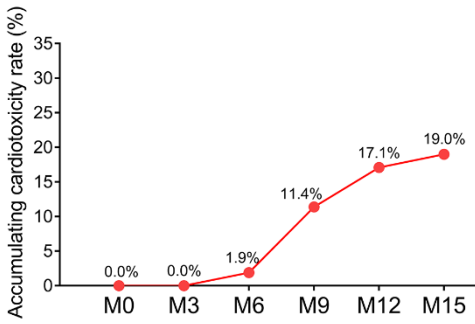

Figure 2. Accumulating cardiotoxicity rate in HER2⁺ breast cancer patients. HER2⁺: human epidermal receptor 2 positive; M: month.

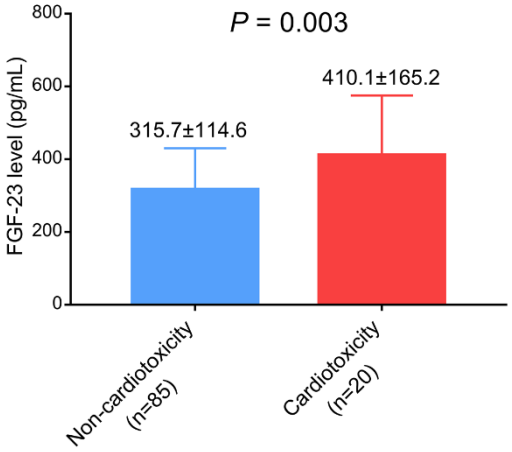

Figure 3. Comparison of FGF-23 level between non-cardiotoxicity and cardiotoxicity patients. FGF-23: fibroblast growth factor 23.

icity, while LVEF (p=0.047) was correlated with reduced risk of cardiotoxicity. Subsequent multivariate logistic regression analysis displayed that FGF-23 (p=0.021) was an independent risk factor predicting cardiotoxicity, also, age (p=0.011) could independently predict increased risk of cardiotoxicity (Table 4). Furthermore, we performed ROC curves to further monitor the value of independent factors for predicting cardiotoxicity risk, which disclosed that FGF-23 (AUC: 0.664; 95%CI: 0.529-0.799) and age (AUC: 0.722; 95%CI: 0.627-0.816) could predict cardiotoxicity risk. Furthermore, the combination of FGF-23 and age had a good predictive value for cardiotoxicity risk (AUC: 0.768, 95%CI: 0.664-0.872) (Figure 4).

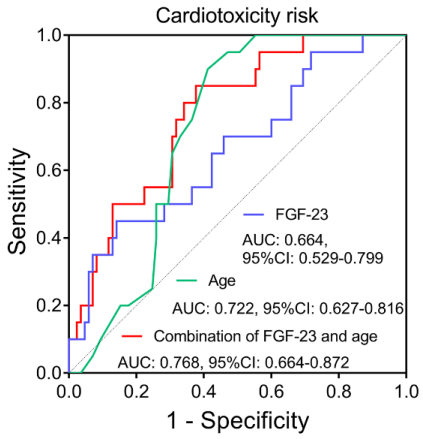

Figure 4. The value of independent factors predicting cardiotoxicity risk assessed by ROC curves. FGF-23: fibroblast growth factor 23; AUC: area under curve; CI: confidence interval; ROC: Receiver operating characteristic.

Discussion

FGF-23, a bone-derived hormone, has been originally identified as a negative feedback on the stimulation of vitamin D and promotes phosphate excretion, which also is considered as having a key role involved in the cardiotoxicity pathology of various diseases [7]. For example, an interesting study displayed that FGF-23 contributed to the pathologic hypertrophy of isolated rat cardiomyocytes via FGF receptor-dependent activation of the calcineurin–nuclear factor of activated T cells (calcineurin-NFAT) signaling pathway *in vitro*, and then the injection of FGF-23 also induced the myocyte hypertrophy and left ventricular hypertrophy (LVH) *in vivo* [8]. Meanwhile, FGF-23 has been found to directly mediate the membrane abundance of the Na(+):Cl(-) co-transporter Na-Cl co-transporter

Table 4. Logistic regression analysis of factors associated with cardiotoxicity

Logistic regression analysis							
Parameters	*Beta*	*S.E.*	*Wald*	*p value*	*OR*	*95% CI*	
						Lower	*Upper*
Univariate logistic regression							
FGF-23	0.005	0.002	7.405	0.007	1.005	1.001	1.009
Age	0.117	0.041	8.179	0.004	1.124	1.037	1.218
BMI	0.147	0.105	1.946	0.163	1.158	0.942	1.423
Smoker	0.613	0.598	1.052	0.305	1.846	0.572	5.959
Hypertension	1.187	0.563	4.444	0.035	3.276	1.087	9.872
Hyperlipidemia	1.166	0.636	3.358	0.067	3.208	0.922	11.162
Diabetes mellitus	1.274	0.809	2.478	0.115	3.574	0.732	17.447
Hyperuricemia	0.808	0.609	1.757	0.185	2.242	0.680	7.400
Chromic kidney disease	1.038	0.778	1.782	0.182	2.824	0.615	12.962
ECOG PS=1	0.693	0.565	1.506	0.220	2.000	0.661	6.051
LVEF	-0.142	0.071	3.957	0.047	0.868	0.755	0.998
cTnI	0.016	0.007	5.306	0.021	1.017	1.002	1.031
NT-proBNP	0.013	0.007	4.148	0.042	1.014	1.001	1.027
Multivariate logistic regression (forward stepwise: conditional)							
FGF-23	0.005	0.002	5.331	0.021	1.005	1.001	1.009
Age	0.106	0.042	6.495	0.011	1.112	1.025	1.207

OR: odds ratio; CI: confidence interval; FGF-23: fibroblast growth factor 23; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; LVEF: left ventricular ejection fraction; cTnI: cardiac troponin I; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

(NCC) in distal renal tubules through a signaling mechanism involving the FGF receptor/αKlotho complex, extracellular signal-regulated kinase 1/2 (ERK1/2), serum/glucocorticoid-regulated kinase 1 (SGK1), and with-no lysine kinase-4 (WNK4), subsequently stimulating sodium re-absorption and volume expansion in CKD *in vivo* [15]. Taken together, these previous reports suggest the promotive influence of FGF-23 underlying cardiotoxicity pathology of various diseases *in vivo* and *in vitro*.

Apart from the potential mechanism of FGF-23 underlying cardiotoxicity pathology of various diseases, several studies have been carried out to investigate the clinical value of FGF-23, which displayed that FGF-23 is upregulated and related to several different forms of cardiovascular events in CKD patients [16], type 2 diabetes mellitus patients [17] and peritoneal dialysis patients [18], whereas few studies have been performed to explore the expression of FGF-23 and its correlation with cardiotoxicity risk induced by treatment in cancer patients, including HER2+ breast cancer patients receiving adjuvant EC->D+T treatment. In the current study, we found that the mean FGF-23 level was 333.7±130.3 pg/ml in HER2+ breast cancer patients, and it was correlated with hypertension, CKD, decreased LVEF, increased cTnI and higher NT-proBNP. The possible explanations were as follows: (1) Regarding hypertension: FGF-23 might promote sodium reabsorption and volume expansion via NCC in the distal convoluted tubule, thereby increased high risk of hypertension in HER2+ breast cancer patients [15]. (2) Regarding CKD, FGF-23 has been reported to be the first mineral metabolic marker changing in CKD, and its level increased as CKD progressed, hence, FGF-23 was related to CKD in HER2+ breast cancer patients [19]. (3) Regarding LVEF, cTnI and NT-proBNP: FGF-23 might regulate several metabolism-related factors (including fibroblast growth factor receptors and phosphate induced vascular calcification) related to cardiotoxicity risk, thus, FGF-23 high level was correlated to decreased LVEF, increased cTnI and raised NT-proBNP) in HER2+ breast cancer patients [16,20,21].

Several studies clarify that both HER2 targeted blocking agents and chemotherapy have obviously improved survival in HER2+ breast cancer patients, while their cardiotoxic side effects risk also cannot be ignored [12,22]. A recent study reveals that trastuzumab plus chemotherapy increases the risk of congestive heart failure and decreases LVEF (11.2% *vs.* 5.6%) compared to chemotherapy alone [6]. Meanwhile, another previous study discloses that the combination of chemotherapy and trastuzumab treatment causes a 2-fold increased risk of late heart failure compared with chemotherapy alone in breast cancer patients (3.3% *vs.* 1.3%) [5]. In this study, we discovered the accumulation cardiotoxicity rate was 19.0% in HER2+ breast cancer patients receiving adjuvant EC->D+T treatment. This finding was similar with previous data [23]. From accumulating evidence, elevated FGF-23 levels have been reported to be related to several different forms of cardiovascular events in patients with various diseases. For instance, a recent study illustrates that elevated FGF23 is correlated with greater left ventricular mass and greater prevalence of LVH in CKD patients [16]. Meanwhile, a previous study enrolled 282 patients with type 2 diabetes mellitus but without significant kidney disease, which showed that high FGF-23 level was related to increased risk of coronary artery calcified atherosclerotic plaque [17]. Another study displayed a correlation of FGF-23 high level with higher carotid artery intima-media thickness (another marker of subclinical atherosclerosis) in peritoneal dialysis patients [18]. However, little was known about the influence of FGF-23 on cancer-related cardiotoxicity and treatment-induced cardiotoxicity. In our study, we found that FGF-23 level was higher in cardiotoxicity patients compared with non-cardiotoxicity patients, and it was an independent risk factor predicting adjuvant EC->D+T treatment-induced cardiotoxicity in HER2+ breast cancer patients. The plausible explanations were that: (1) FGF-23 could regulate several pathways (such as calcineurin-NFAT signaling pathway) to stimulate the myocyte hypertrophy and left ventricular hypertrophy (LVH), eventually increased cardiotoxicity risk in HER2+ breast cancer patients [8]. (2) FGF-23 might non-selectively activate fibroblast growth factor receptors implicated in the development of cardiac hypertrophy and atherosclerosis, thereby increased cardiotoxicity risk in HER2+ breast cancer patients [16,20]. (3) FGF-23 activated phosphate-induced vascular calcification to promote aortic cells to differentiate into osteoblastic cells, thereby enhanced vascular calcification and increased cardiotoxicity risk in HER2+ breast cancer patients [21]. (4) FGF-23 might be associated with high risk of hypertension through stimulated sodium reabsorption and volume expansion, which was related to atherosclerosis and vascular dysfunction, thereby increased cardiotoxicity risk in HER2+ breast cancer patients [7,15]. (5) As the above mentioned, FGF-23 could regulate multiple ways to promote heart injury, and its high level was related to high risk of cardiotoxicity in breast cancer patients. In this situation, further receiving adjuvant EC->D+T treatment might decrease the drug tolerance in those HER2+ breast cancer patients, thereby increasing their cardiotoxicity risk.

Therefore, FGF-23 was correlated with increased cardiotoxicity risk induced by adjuvant EC->D+T treatment in HER2+ breast cancer patients.

Our study has several limitations. One major limitation was the relatively small sample size which might lead to poor statistical significance. This problem might be due to that the overall economic income of the patient areas covered by our hospital was relatively low, which affected patients to continually receive trastuzumab treatment. Thus, further multicenter studies enrolling more HER2+ breast cancer patients receiving adjuvant EC->D+T treatment are urgently needed. The second main limitation was that continual monitor of FGF-23 level might better promote the management of adjuvant EC->D+T treatment-induced cardiotoxicity in HER2+ breast cancer patients, which it was not explored in this study. Thus, further relevant studies are needed.

To sum up, FGF-23 is upregulated and correlates with hypertension, CKD and poor cardiac function, and more importantly, it is an independent risk factor predicting adjuvant EC->D+T treatment-induced cardiotoxicity in HER2+ breast cancer patients.

Conflict of interests

The authors declare no conflict of interests.

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