Original Article

Cardiotoxicity monitoring of pyrotinib in combination with nab-paclitaxel, doxorubicin, and cyclophosphamide in HER2-positive breast cancer: a single-armed clinical trial

Wei Wang[1,2], Lu Wang[1], Jin-Yi Chang[1,2], Fen Hu[3], Jin-Yin Yan[4], Juan Zhang[1], Yong-Ping Liang[5], Hui-Wen Zhang[6], Hong-Peng Wu[7], Hai-Feng Cai[1]

[1]Department of Breast Surgery, Tangshan People's Hospital, North China University of Science and Technology, Tangshan, China; [2]School of Clinical Medicine, North China University of Science and Technology, Tangshan, China; [3]College of Life Sciences, North China University of Science and Technology, Tangshan, China; [4]Department of Breast Surgery, Tangshan Central Hospital, Tangshan, China; [5]Department of Medical Imaging (Ultrasound), Tangshan People's Hospital, Tangshan, China; [6]College of Nursing and Rehabilitation, North China University of Science and Technology, Tangshan, China; [7]Tangshan Jianhua Technology Development Limited Liability Company, Tangshan, China

Contributions: (I) Conception and design: HF Cai; (II) Administrative support: HF Cai; (III) Provision of study materials or patients: W Wang, L Wang, JY Chang, F Hu, JY Yan, HP Wu, J Zhang, YP Liang; (IV) Collection and assembly of data: W Wang, L Wang, JY Chang, HP Wu, J Zhang, HW Zhang; (V) Data analysis and interpretation: W Wang, L Wang, J Zhang, JY Chang, HW Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hai-Feng Cai. Department of Breast Surgery, Tangshan People's Hospital, North China University of Science and Technology, Shengli Road 65, Tangshan 063000, China. Email: 13303050005@163.com.

Background: Human epidermal growth factor receptor 2 (HER2) inhibitors play a vital role in the treatment of HER2-positive breast cancer. Numerous studies have shown that traditional HER2 inhibitors and chemotherapeutics such as albumin-paclitaxel, liposomal doxorubicin, and cyclophosphamide (TAC regimen) have different degrees of cardiotoxicity. Pyrotinib is a novel small-molecule HER2 inhibitor and has no cardiotoxicity. Here, the purpose of this study was to investigate the cardiac safety of pyrotinib with TAC regimen for HER2-positive breast cancer.

Methods: In this study, 22 patients with stage I–IIIA HER2-positive breast cancer were screened, enrolled, and assigned to receive either neoadjuvant or postoperative adjuvant treatment with pyrotinib (320–400 mg, once daily) combined with TAC (albumin-paclitaxel 260 mg/m^2, liposomal doxorubicin 20 mg/m^2, cyclophosphamide 600 mg/m^2) from December 2019 to May 2021. Patients' heart function was monitored using electrocardiogram, echocardiogram, and serological indicators. ST segment and T wave change, left ventricular ejection fraction (LVEF, %), N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), creatine kinase (CK), creatine kinase myoglobin band (CK-MB), together with patients' weight, white blood cells (WBC), red blood cells (RBC), platelets, plasma lipid, and glucose were recorded.

Results: Before and after the 2nd, 4th, and 6th cycles of treatment, the incidence of abnormal electrocardiogram of patients enrolled in the neoadjuvant treatment group was 36.4%, 27.3%, 27.3%, and 27.3%, respectively, while in the postoperative adjuvant treatment, the incidence was 45.5%, 36.4%, 36.4%, and 36.4%, respectively. LVEF before and after treatment in the neoadjuvant chemotherapy group was 65.36%±2.25% and 65.00%±2.15% (t=1.305, P=0.221), while in the postoperative adjuvant treatment group, LVEF was 66.27%±2.69% and 65.18%±1.89% (t=1.359, P=0.204). Pyrotinib combined with a TAC regimen may have induced a decrease in RBC. No obvious abnormality was found in the level of NT-pro-BNP, CK, CK-MB, patients' weight, WBC, platelets, plasma lipid, or glucose in all enrolled patients during the entire treatment process.

Conclusions: Our findings indicated that neither neoadjuvant nor postoperative adjuvant treatment using pyrotinib combined with a TAC regimen to treat patients with HER2-positive breast cancer increased cardiotoxicity. However, the treatment may have induced a decrease in RBC and further research is needed.

Keywords: Cardiotoxicity; pyrotinib; HER2-positive breast cancer; chemotherapy

Submitted Feb 22, 2022. Accepted for publication Apr 14, 2022.
doi: 10.21037/gs-22-161
View this article at: https://dx.doi.org/10.21037/gs-22-161

Introduction

The human epidermal growth factor receptor 2 (HER2) is a proto-oncogene located on the long arm of human chromosome 17 and is found to be positive in multiple cancers (1). Previous studies have demonstrated HER2 overexpression is associated with poor prognosis in patients with breast cancer (2,3). Thus, anti-HER2 therapies play an important role in treating HER2-positive breast cancer.

Currently, treatment for HER2-positive breast cancer is mainly based on chemotherapy combined with HER2-targeted therapy (1). The combination of albumin-paclitaxel, liposomal doxorubicin, and cyclophosphamide (TAC) is a common and effective chemotherapy regimen for the treatment of patients with breast cancer. However, anthracycline and cyclophosphamide may lead to cardiotoxicity (4). Anthracycline drugs (such as doxorubicin, doxorubicin, epirubicin), mainly due to the formation of reactive oxygen species and affect mitochondrial biosynthesis, resulting in cardiac damage (5). With developments in medical science, a variety of new targeted drugs have emerged, including trastuzumab, pertuzumab, trastuzumab emtansine (T-DM1), neratinib, lapatinib, and pyrotinib. Among them, trastuzumab has been recognized as a standard treatment for HER2-positive breast cancer since 2002. HER2-targeted therapies have improved patient outcomes; however, cardiotoxicity is very common during treatment (6). Trastuzumab binds to HER2 protein and inhibits cell growth signaling, leading to structural and functional changes in myocardial contractile proteins and mitochondria, resulting in non-dose-dependent and reversible cardiac dysfunction (7). In clinical breast cancer patients, cardiac function needs to be monitored and evaluated repeatedly during chemotherapy. If cardiac insufficiency occurs during treatment, conventional anti-heart failure therapy should be taken immediately. Use diuretics, β-receptor blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blocker (ARB) and other anti-arrhythmia drugs according to the patient's situation. Although most patients improve with treatment and can continue to receive treatment. Nonetheless, treatment for patients with HER2-positive breast cancer remains challenging clinically due to cardiotoxicity.

Pyrotinib is a small-molecule irreversible tyrosine kinase inhibitor (8) which has been proven to be effective and safe in patients with HER2-positive advanced breast cancer when used alone or in combination with chemotherapy drugs (9,10). Nevertheless, to date, there is a lack of studies on the efficacy and safety of pyrotinib combined with chemotherapy, especially TAC, in patients with early-stage HER2-positive breast cancer. In addition, cardiotoxicity in breast cancer patients with anti-HER2 therapy has been the focus of previous studies. Thus, we conducted this study to investigate the safety, and cardiotoxicity in particular, of pyrotinib combined with a TAC regimen for treating patients with early-stage HER2-positive breast cancer. We present the following article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-161/rc).

Methods

Patients

In this study, patients with stage I–IIIA HER2-positive breast cancer who were admitted to the Second Department of Breast Surgery, Tangshan People's Hospital between December 15, 2019 and May 15, 2021 were screened. Inclusion criteria: (I) patients diagnosed with stage I–IIIA HER2-positive breast cancer (immunochemical 3+ or immunochemical 2+, fluorescence *in situ* hybridization confirmed HER2 gene amplification); (II) patients aged 31–65 years old; (III) patients with an Eastern Cooperative Oncology Group (ECOG) score of 0 to 1; (IV) patients with main organ (heart, liver, kidney) function able to tolerate the treatment of pyrotinib + TAC; and (V) patients who agreed to participate. Exclusion criteria: (I) patients with advanced breast cancer; (II) patients with drug allergy or taking other drugs that affected absorption; (III) patients with serious heart, liver, kidney, or endocrine disease; and (IV) patients who did not wish to participate. The

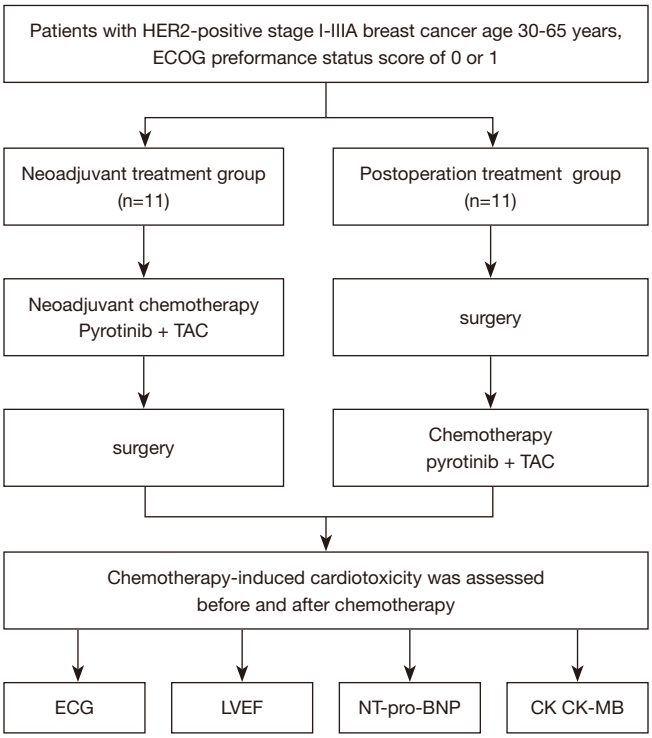

Figure 1 Trial design. Pyrotinib: 320–400 mg, once daily; TAC: albumin-paclitaxel 260 mg/m^2 +liposomal doxorubicin 20 mg/m^2 + cyclophosphamide 600 mg/m^2; 4–6 cycles of chemotherapy, each cycle was 21 days. ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; CK, creatine kinase; CK-MB, creatine kinase myoglobin band.

trial protocol was approved by the Ethics Committee of Tangshan People's Hospital (No. RMYY-LLKS-2021-109). All patients offered written informed consent before being screened for potential recruitment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Treatment strategy

Eligible patients were divided into a neoadjuvant and postoperative adjuvant treatment group according to the patients' conditions (*Figure 1*). Patients in the neoadjuvant treatment group received 4 to 6 cycles of pyrotinib combined with the TAC regimen followed by surgery, and patients in the postoperative adjuvant treatment group underwent surgery followed by 4 to 6 cycles of pyrotinib combined with the TAC regimen. All patients received relevant examinations, including blood routine, biochemical routine, tumor markers, electrocardiogram, myocardial enzyme, ultrasound and other examinations, before each admission for chemotherapy as well as before and after surgery. Follow-up was conducted once every three months within two years after surgery, however, in this study, patients were only followed up to one month after surgery or the end of chemotherapy cycle. Pyrotinib (320–400 mg) was given once per day orally, accompanied by albumin-paclitaxel (260 mg/m^2), liposomal doxorubicin (20 mg/m^2), and cyclophosphamide (600 mg/m^2) intravenously in a cycle of 21 days. Information of the drugs used in this study is shown in *Table 1*.

Outcomes

The primary outcome of this study was cardiotoxicity defined as abnormal electrocardiogram (ECG) (T wave change, ST segment change, abnormal Q wave, left ventricular high voltage, reverse clock transposition, and left deviation of ECG axis), left ventricular ejection fraction (LVEF), N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), creatine kinase (CK), and creatine kinase

Table 1 Drug information

Drug name	Drug dosage	Drug use	Company name
Pyrotinib	320–400 mg	Continuous administration from day 1 of the first course, once daily, 46 cycles, each cycle was 21 days	Jiangsu Hengrui Medicine
Albumin-paclitaxel	260 mg/m^2	Intravenous injection, repeated every 21 days, 4–6 cycles	Jiangsu Hengrui Medicine
Liposomal doxorubicin	20 mg/m^2	Intravenous injection, repeated every 21 days, 4–6 cycles	China Stone Pharmaceuticals Group
Cyclophosphamide	600 mg/m^2	Intravenous injection, repeated every 21 days, 4–6 cycles	Jiangsu Hengrui Medicine

myoglobin band (CK-MB). The secondary outcome of this study was the effect on other indicators, including weight, blood routine, plasma lipid, and glucose. ECG was assessed before and after the 2nd, 4th, and 6th cycles of treatment, while LVEF, NT-pro-BNP, CK, and CK-MB were assessed before and after treatment.

Statistical analyses

Descriptive statistical methods were used to analyze the data. Data are expressed as median (range), frequency (n%), or mean ± standard deviation (SD), as appropriate, and SPSS software (SPSS 17.0) was used for analysis. Normally distributed variables were compared using paired *t* test, and if they were not normally distributed, Mann-Whitney test was used. Incidence of abnormal ECG, NT-pro-BNP, CK, and CK-MB values were compared using Chi-square test. P<0.05 was considered to indicate statistical significance. P<0.05 is two-sided.

Results

Characteristics of patients

Between December 15, 2019 and May 15, 2021, a total of 22 eligible female patients [age range: 30–65; body mass index (BMI) range: 17.40–34.90] with stage I–IIIA HER2-positive breast cancer were enrolled in this study. The patients were divided into a neoadjuvant treatment group (n=11, 50%) and postoperative adjuvant treatment group (n=11, 50%), based on the patients' conditions. Among them, 21 patients were pathologically classified as invasive ductal carcinoma, while 1 patient was pathologically classified as cellular mucinous carcinoma and papillary carcinoma. All enrolled patients completed the entire study. The characteristics of the patients at baseline were similar in the 2 groups (*Table 2*).

ECG and LVEF changes

In the neoadjuvant treatment group, 4 patients had a minor abnormal ECG before receiving pyrotinib plus TAC regimen, and among them, only 1 patient had an abnormal ECG during treatment. In patients who had a normal ECG before treatment, 1 patient had an abnormal ECG after the second, fourth, and sixth cycles of treatment, and 1 had an abnormal ECG after the second and fourth cycles of treatment. The incidence of abnormal ECG was 36.4% (4/11), 27.3% (3/11), 27.3% (3/11), and 27.3% (3/11) after each treatment cycle, respectively. In the postoperative adjuvant treatment group, 5 patients had a minor abnormal ECG before the treatment, and among them, 4 patients had an abnormal ECG during treatment. One patient with normal ECG before treatment had an abnormal ECG after the second, fourth, and sixth cycles of therapy. Overall, the incidence of abnormal ECG was 45.5% (5/11), 36.4% (4/11), 36.4% (4/11), and 36.4% (4/11) after each treatment cycle, respectively. Of note, the incidence of abnormal ECG was not significantly different during treatment in both groups (χ^2=0.058, P=0.996) (*Table 3*).

LVEF (%) in both the neoadjuvant treatment group (65.36±2.25 *vs.* 65.00±2.15; t=1.305; P=0.221) and the postoperative adjuvant treatment group (66.27±2.69 *vs.* 65.18±1.89; t=1.359; P=0.204) decreased during treatment, but there were no significant differences before and after treatment in the 2 groups (*Figure 2*).

Plasma NT-pro-BNP, CK, and CK-MB changes

In the neoadjuvant treatment group, 3 patients had abnormal NT-pro-BNP values before treatment, and among them, 2 patients experienced abnormal NT-pro-BNP values once during treatment, after which, their NT-pro-BNP values returned to normal without any treatment. In patients with normal NT-pro-BNP values before neoadjuvant treatment, 2 patients' NT-pro-BNP

Table 2 Patient baseline characteristics

Characteristics	Neoadjuvant treatment group (n=11)	Postoperative adjuvant treatment group (n=11)	Total (n=22)
Age (years)			
Median/range	55 [31–65]	56 [30–63]	55 [30–65]
BMI (kg/m^2)			
BMI <18.5	1	0	1
18.5≤ BMI <24	2	7	9
24≤ BMI <28	4	3	7
BMI ≥28	4	1	5
Eastern Cooperative Oncology Group performance status			
0	9	6	15
1	2	5	7
Tumor site			
≤2 cm	3	3	6
>2 to ≤5 cm	8	5	13
>5 cm	0	3	3
Previous anti-HER2 antibody treatment			
Yes	0	1	1
No	11	10	21
Hormone receptor status			
Negative ER and PR	4	6	10
Positive ER or positive PR	7	5	12
Pathological types			
IDC	11	10	21
Other	0	1	1

BMI, body mass index; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; IDC, invasive ductal carcinoma.

values had transient abnormality during the treatment and 1 patient had abnormal NT-pro-BNP values after treatment. In the postoperative adjuvant treatment group, all patients had normal NT-pro-BNP values before treatment, and 2 patients' NT-pro-BNP values had transient abnormality during treatment. Meanwhile, 1 patient had abnormal NT-pro-BNP values after treatment (P=1.000) (*Table 4*). Ten patients had abnormal CK values during treatment, and 1 of them had abnormal CK values more than twice. Values of CK-MB for all patients remained normal during treatment.

Red blood cell (RBC) changes

RBC decreased significantly in both the neoadjuvant (4.64±0.46 *vs.* 4.26±0.27; Z=–2.136, P=0.034) and the postoperative adjuvant settings (4.63±0.48 *vs.* 3.97±0.45; Z=–2.725, P=0.005); however, they were still within normal range. In addition, pyrotinib combined with a TAC regimen had no effect on patients' weight, white blood cells (WBC), platelets (PLT), plasma lipid, and glucose (*Table 5*).

Discussion

In our study, there were no significant differences in ECG, LVEF, NT-pro-BNP, CK, CK-MB, weight, WBC, PLT, plasma lipid, and glucose in HER2-positive breast cancer patients treated with pyrotinib in combination with a TAC regimen in either neoadjuvant or postoperative adjuvant

Table 3 Electrocardiogram monitoring

Patients	Before	After 2 cycles	After 4 cycles	After 6 cycles
A	0	0	0	0
B	1	0	0	0
C	0	0	0	0
D	0	1	1	1
E	0	0	0	0
F	1	0	0	0
G	0	0	0	0
H	1	1	1	1
I	1	0	0	0
J	0	0	0	0
K	0	1	1	0
L	0	0	0	0
M	1	1	1	1
N	0	0	0	0
O	0	0	0	0
P	1	1	1	1
Q	0	0	0	0
R	1	0	0	0
S	1	1	1	1
T	0	1	1	1
U	1	0	0	0
V	0	0	0	0

0: normal electrocardiogram; 1: electrocardiogram abnormality. A-K, neoadjuvant treatment group; L-V, postoperative adjuvant treatment group.

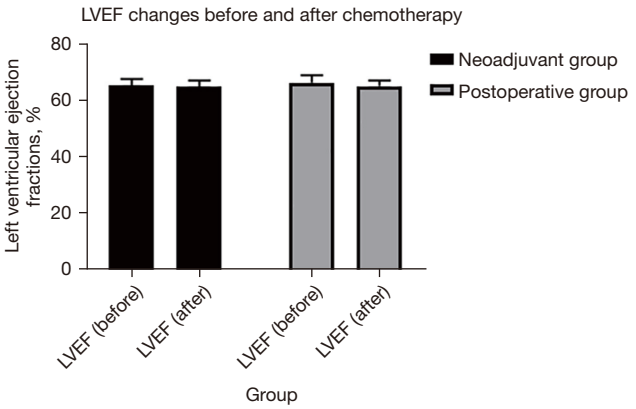

Figure 2 LVEF changes before and after chemotherapy. Paired t test, neoadjuvant group: 65.36±2.25 and 65.00±2.15 (t=1.305, P=0.221); postoperative group before and after treatment LVEF was 66.27±2.69 and 65.18±1.89 (t=1.359, P=0.204). LVEF, left ventricular ejection fraction.

settings. However, a decreasing trend in RBC was shown after patients underwent treatment. Overall, our data showed pyrotinib combined with a TAC regimen did not increase cardiotoxicity and was safe for use.

Breast cancer has become the most common malignant tumor in women all over the world (11). Nearly 25% of breast cancers overexpress HER2, which is associated with higher recurrence risk and decreased survival (12). Mounting evidence has shown that an anti-HER2 regimen is vital in treating HER2-positive breast cancer (13-19). However, cardiotoxicity is a common adverse effect induced by HER2-targeted therapies (20). It has been reported that 4.0–18.6% of patients treated with HER2-targeted therapies combined with anthracyclines had decreased LVEF and 0.4–4.1% had severe heart failure, while there was 3.2% LVEF decline and 0.5% symptomatic heart failure when anthracyclines were absent (21,22).

The principle of prevention and management of HER2-targeted agent-associated cardiotoxicity is mainly based on using neurohormonal antagonist medications [such as beta-adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs)], controlling cardiovascular risk factors (e.g., hypertension and diabetes), and monitoring cardiac function during treatment (20).

In cardiac monitoring, LVEF can reflect the contractility of myocardium, which is an important indicator for making decisions to cease or interrupt treatment (23). Biomarkers are also important indicators for detecting cardiotoxicity. NT-pro-BNP can predict cardiotoxicity, and CK and CK-MB can reflect myocardial injury when CK value exceeds 2 times the normal value together with an abnormal CK-MB value (12). In our study, no obvious changes were revealed in ECG, LVEF, NT-pro-BNP, CK, or CK-MB. However, patients' RBC decreased significantly in both groups, and while they were still within normal range, further attention is required for future use. Pyrotinib combined with a TAC regimen also had no effect on patients' weight, WBC, PLT, plasma lipid, or glucose. Our data suggested that pyrotinib combined with a TAC regimen was safe for use in treating patients with HER2-positive breast cancer.

The mechanisms of HER2-targeted therapy-associated

Table 4 Number of patients with abnormal BNP

Number of patients with abnormal BNP	Number of patients with abnormalities before treatment		Number of patients with abnormalities after treatment		Number of patients with abnormalities during treatment	
	Neoadjuvant treatment group	Postoperative adjuvant treatment group	Neoadjuvant treatment group	Postoperative adjuvant treatment group	Neoadjuvant treatment group	Postoperative adjuvant treatment group
NT-pro-BNP	3	0	1	1	4	2
Total	3		2		6	

NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

Table 5 Other indicators

Indicators	Neoadjuvant treatment group (n=11)				Postoperative adjuvant treatment group (n=11)			
	Before	After	Z	P	Before	After	Z	P
Weight, kg	70.18±18.07	68.18±15.81	−0.329	0.748	58.36±10.70	58.91±10.56	−0.132	0.898
WBC	7.49±2.93	5.58±2.62	−1.543	0.133	6.97±1.51	5.91±2.10	−1.346	0.193
RBC	4.64±0.46	4.26±0.27	−2.136	0.034	4.63±0.48	3.97±0.45	−2.725	0.005
PLT	293.09±72.66	294.91±108.13	−0.230	0.847	280.82±41.01	257.64±49.00	−0.788	0.438
GLU	6.87±2.20	6.97±1.72	−0.296	0.797	6.90±2.32	6.35±1.82	−0.755	0.478
TC	5.85±1.26	6.35±1.82	−0.427	0.699	5.89±1.37	5.39±1.38	−0.952	0.365
TG	1.57±1.08	2.32±1.48	−1.281	0.217	1.60±0.68	2.10±1.47	−0.460	0.652
HDL	1.61±0.41	1.43±0.36	−1.150	0.270	1.61±0.27	1.55±0.40	−0.953	0.365
LDL	3.36±0.93	3.47±1.00	−0.033	1.000	3.30±1.08	2.80±0.86	−1.280	0.217

P<0.05 was considered to be statistically significant. WBC, white blood cell; RBC, red blood cell; PLT, platelet; GLU, glucose; TC, serum total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; Z, values of standardized Wilcoxon statistics.

cardiotoxicity remain unclear. It may be due to a protective function disruption or HER2 signaling interference. However, cardiotoxicity was not observed in the ExteNET study, in which patients with HER2-positive breast cancer were treated with neratinib. This could be associated with the patients' inclusion criteria (20). Similar to neratinib, pyrotinib is a small-molecule irreversible tyrosine kinase inhibitor (8) and has been proven to be effective and safe when used alone or in combination with chemotherapy drugs in patients with HER2-positive advanced breast cancer (9,10). In the present study, there were some enrolled patients with an abnormal ECG or NT-pro-BNP, yet no obvious cardiotoxicity was observed during or after the administration of treatment. This suggested pyrotinib combined with a TAC regimen did not increase cardiotoxicity as either neoadjuvant or postoperative adjuvant treatment for patients with HER2-positive breast cancer.

The limitations of this study are as follows: firstly, the sample size was small and may not be able to fully represent all patients with HER2-positive breast cancer; and secondly, due to a lack of data from long-term follow-up, the long-term effects on cardiac function are still unknown.

Conclusions

In summary, this single-armed clinical study demonstrated pyrotinib combined with a TAC regimen in the treatment of patients with HER2-positive breast cancer did not increase cardiotoxicity in either the neoadjuvant or adjuvant setting. Further, this treatment regimen did not affect patients' weight, WBC, PLT, plasma lipid, or glucose. However, it may have induced a decrease in RBC and further research is needed to verify this result.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-161/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-161/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-161/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Tangshan People's Hospital (No. RMYY-LLKS-2021-109) and informed consent was taken from all the patients.

References

1. Early Breast Cancer Trialists' Collaborative group (EBCTCG). Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. Lancet Oncol 2021;22:1139-50.
2. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177-82.
3. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol 2009;27:5700-6.
4. von Minckwitz G, Blohmer JU, Costa SD, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol 2013;31:3623-30.
5. Kong CY, Guo Z, Song P, et al. Underlying the Mechanisms of Doxorubicin-Induced Acute Cardiotoxicity: Oxidative Stress and Cell Death. Int J Biol Sci 2022;18:760-70.
6. Hussain Y, Drill E, Dang CT, et al. Cardiac outcomes of trastuzumab therapy in patients with HER2-positive breast cancer and reduced left ventricular ejection fraction. Breast Cancer Res Treat 2019;175:239-46.
7. Barish R, Gates E, Barac A. Trastuzumab-Induced Cardiomyopathy. Cardiol Clin 2019;37:407-18.
8. Blair HA. Pyrotinib: First Global Approval. Drugs 2018;78:1751-5.
9. Ma F, Li Q, Chen S, et al. Phase I Study and Biomarker Analysis of Pyrotinib, a Novel Irreversible Pan-ErbB Receptor Tyrosine Kinase Inhibitor, in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol 2017;35:3105-12.
10. Ma F, Ouyang Q, Li W, et al. Pyrotinib or Lapatinib Combined With Capecitabine in HER2-Positive Metastatic Breast Cancer With Prior Taxanes, Anthracyclines, and/or Trastuzumab: A Randomized, Phase II Study. J Clin Oncol 2019;37:2610-9.
11. Cheung YF, Hong WJ, Chan GC, et al. Left ventricular myocardial deformation and mechanical dyssynchrony in children with normal ventricular shortening fraction after anthracycline therapy. Heart 2010;96:1137-41.
12. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-92.
13. Burstein HJ, Sun Y, Dirix LY, et al. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. J Clin Oncol 2010;28:1301-7.
14. Dieras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA). A descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:732-42.

15. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.
16. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.
17. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278-84.
18. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016;17:367-77.
19. Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1688-700.
20. Copeland-Halperin RS, Liu JE, Yu AF. Cardiotoxicity of HER2-targeted therapies. Curr Opin Cardiol 2019;34:451-8.
21. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015;372:134-41.
22. Dang C, Guo H, Najita J, et al. Cardiac Outcomes of Patients Receiving Adjuvant Weekly Paclitaxel and Trastuzumab for Node-Negative, ERBB2-Positive Breast Cancer. JAMA Oncol 2016;2:29-36.
23. Jordan JH, Sukpraphrute B, Meléndez GC, et al. Early Myocardial Strain Changes During Potentially Cardiotoxic Chemotherapy May Occur as a Result of Reductions in Left Ventricular End-Diastolic Volume: The Need to Interpret Left Ventricular Strain With Volumes. Circulation 2017;135:2575-7.

(English Language Editor: A. Muijlwijk)

Cite this article as: Wang W, Wang L, Chang JY, Hu F, Yan JY, Zhang J, Liang YP, Zhang HW, Wu HP, Cai HF. Cardiotoxicity monitoring of pyrotinib in combination with nab-paclitaxel, doxorubicin, and cyclophosphamide in HER2-positive breast cancer: a single-armed clinical trial. Gland Surg 2022;11(4):742-750. doi: 10.21037/gs-22-161