Efficacy, toxicity and prognostic factors of pyrotinib-involved neoadjuvant therapy in HER2-positive breast cancer: A retrospective study

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Abstract. Pyrotinib is a novel irreversible tyrosine kinase inhibitor targeting the human epidermal growth factor receptor (HER), whose efficacy in treating metastatic HER2-positive ($HER2^+$) breast cancer has been confirmed. The present study aimed to explore the efficacy, safety and prognostic factors of pyrogenic-involved neoadjuvant therapy in patients with $HER2^+$ breast cancer. A total of 49 patients with $HER2^+$ breast cancer who received pyrotinib-neoadjuvant therapy were recruited. All patients received pyrotinib plus chemotherapy with or without trastuzumab neoadjuvant treatment for six cycles (21 days/cycle). Concerning the clinical response, 4 (8.2%), 36 (73.4%) and 9 (18.4%) patients achieved complete response, partial response and stable disease after 6-cycle pyrotinib-neoadjuvant treatment, respectively; the objective response rate and disease control rate reached 81.6 and 100.0%, respectively. Concerning the pathological response, 23 (46.9%), 12 (24.5%), 12 (24.5%) and 2 (4.1%) patients were evaluated as Miller-Payne grade 5, 4, 3 and 2, respectively. In addition, 23 (46.9%) patients achieved pathological complete response (pCR) in the breast tissue, 40 (81.6%) patients achieved pCR in lymph nodes, while 22 (44.9%) patients obtained total pCR (tpCR). Further multivariate logistic regression analysis demonstrated that pyrotinib plus trastuzumab and chemotherapy (vs. pyrotinib plus chemotherapy) was independently correlated with increased tpCR (P=0.048). The most frequent adverse events included diarrhea (81.6%), anemia (69.4%), nausea and vomiting (63.3%), and fatigue (51.0%). The majority of the adverse events were mild and controllable. In conclusion, pyrotinib-neoadjuvant therapy presented optimal efficacy and mild toxicity in patients with $HER2^+$ breast cancer, whose efficacy was affected by the combination treatment with trastuzumab.

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Introduction

Breast cancer is one of the most prevalent invasive malignancies occurring in female patients, with an estimated 429,105 new cases and 124,002 related deaths in China in 2022 (1,2). Human epidermal growth factor receptor (HER) 2-positive ($HER2^+$) breast cancer is characterized by the overexpression of HER2 (namely ErbB2) and is an aggressive subtype of breast cancer, which accounts for 15-20% of all breast cancer cases worldwide (3,4). Neoadjuvant treatment is recommended for $HER2^+$ breast cancer to reduce tumor load and increase surgical feasibility; moreover, the development and application of HER2-targeted agents, such as pertuzumab and trastuzumab, improve disease-free survival of patients with $HER2^+$ breast cancer (5-7). The KRISTINE and the BERENICE trials showed that neoadjuvant trastuzumab/pertuzumab therapy combined with chemotherapy could improve the total pathological complete response (tpCR) in patients with $HER2^+$ breast cancer (8-10). Based on the aforementioned evidence, HER2-targeted agent-involved neoadjuvant therapy is a reliable treatment selection for patients with $HER2^+$ breast cancer.

Pyrotinib, which was independently developed in China, is a novel, irreversible dual pan-ErbB tyrosine kinase inhibitor, targeting HER1, HER2 and HER4 (11,12). Due to its potent efficacy and tolerable toxicity, pyrotinib combined with chemotherapy was approved for advanced or metastatic $HER2^+$ breast cancer treatment in China (13,14). However, the application of pyrotinib as neoadjuvant therapy in treating $HER2^+$ breast cancer was only reported in a minority of studies (15,16). For example, one recent study disclosed that the objective response rate (ORR) and tpCR reach 100.0 and 45.5%, respectively, following the completion of neoadjuvant pyrotinib plus nab-paclitaxel, liposomal doxorubicin and cyclophosphamide treatment in patients with $HER2^+$ breast cancer (15). An additional study showed that patients with $HER2^+$ breast cancer achieved an ORR of 100.0% and tpCR of 73.7% following neoadjuvant pyrotinib plus epirubicin plus cyclophosphamide treatment and the most common adverse events were diarrhea and leucopenia (16). Nevertheless, the

sample size of the aforementioned studies was relatively small (~20 patients), which further limited the feasibility of the prognostic factor analysis.

Therefore, the present study aimed to explore the efficacy and safety profile of pyrotinib-associated neoadjuvant therapy as well as the applications of its prognostic factors in patients with $HER2^+$ breast cancer.

Materials and methods

Patients. Between June 2020 and March 2022, the present study retrospectively analyzed 49 $HER2^+$ breast cancer patients with pyrotinib-neoadjuvant therapy from Guangzhou Panyu Central Hospital. Among them, 26 (53.1%) patients received pyrotinib plus chemotherapy, and 23 (46.9%) patients were treated with pyrotinib plus trastuzumab and chemotherapy. Patients who met the following criteria were included: i) Those firstly diagnosed with breast cancer; ii) those confirmed as $HER2^+$, which was defined using immunohistochemistry (IHC) (+++ or ++) and by gene amplification via fluorescence *in situ* hybridization (FISH); iii) those who were ≥18 years of age; iv) those who received 6-cycle pyrotinib-neoadjuvant therapy; v) those with a clinical stage of T2-T3/N0-N2/M0; and vi) those with an eastern cooperative oncology group performance status (ECOG PS) 0 or 1. Patients who met the following criteria were excluded: i) Those with an incomplete clinical and pathological response information; and ii) pregnant or lactating patients. The detailed classification of patients was assessed by the corresponding pathologists in the Department of Pathology. The present study was approved by the Ethics Committee of Guangzhou Panyu Central Hospital (approval no. 2021-SR-512). All patients provided written informed consent.

IHC. The tissues were fixed in 4% paraformaldehyde for 24 h at room temperature and embedded in paraffin. Sections were cut to a 4-μm thickness. The sections were then deparaffizined in xylene and rehydrated with serial ethanol. Antigen retrieval was performed by heating in a microwave ovan and blocking with goat serum (Beyotime Institute if Biotechnology) for 30 min at 37˚C. Next, the sections were cultivated with HER2 antibody (1:500; cat. no. 18299-1-AP; Proteintech Group, Inc.) at 4˚C overnight and HRP-conjugated Goat Anti-Rabbit IgG (H+L) (1:1,000; cat. no. SA00001-2; Proteintech Group, Inc.) at 37˚C for 1 h. Finally, the sections were stained with DAB and hematoxylin, and observed with a light microscope (Nikon Corporation).

Recommended therapy regimens. All patients received 6-cycle pyrotinib-neoadjuvant therapy with a 21-day cycle. The recommended therapy regimens included i) pyrotinib plus chemotherapy and ii) pyrotinib plus trastuzumab and chemotherapy. The details of the regimens were reported in recent studies (17,18).

Data collection. The clinical characteristics of the patients were obtained from the hospital's electronic medical records system that was accessed between August 2022 and September 2022. The characteristics specifically included in the present analysis were age, menopausal status, ECOG PS, tumor size, clinical TNM stage, HER2 status, hormone receptor (estrogen receptor and/or progesterone receptor) status and Ki-67 levels. In addition, the clinical TNM stage was assessed via the eighth TNM-based staging of breast cancer (19). The follow-up data were also acquired. The patients were followed up every two treatment cycles since the treatment initiation. During the follow-up, the results of lesion-relevant imaging examinations (after 2-, 4- and 6-cycle therapy), such as chest and lymph node CTs, or color ultrasound were obtained. Based on the aforementioned imaging examination results, the clinical responses corresponding to each time point were evaluated via the response evaluation criteria in solid tumors following a 2-, 4- and 6-cycle therapy (20,21). The clinical responses included complete response (CR), partial response (PR), stable disease (SD) and progression of disease (PD). The ORR and disease control rate (DCR) were calculated according to those clinical responses. In addition, the pathological evaluation of the surgical specimens was retrieved, which was evaluated in the tpCR analysis. The tpCR was determined by taking into account both pathological complete response (pCR) in the breast [by Miller-Payne (MP) grading system] and pCR in the lymph nodes (17). In order to analyze the safety, the adverse events were counted. Notably, the present study did not analyze the cancer tissue, while all evaluations of hormone receptor status, ki-67 levels and pathological evaluation in the surgical specimens were originally completed during treatment and retrieved from the hospital's electronic medical records system for analysis in the current study.

Statistical analysis. SPSS 22.0 (IBM Corp.) was used for data description and processing. GraphPad Prism 7.0 (GraphPad Software; Dotmatics) was used to generate forest plots. Univariate and multivariate logistic regression models were employed to analyze the associated factors to tpCR and to assess the selection of the multivariate model via a forward selection method. The c^2 test was used for comparing the tpCR rate between patients who received pyrotinib plus trastuzumab and chemotherapy and patients who received pyrotinib plus chemotherapy. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics. A total of 49 patients (mean age, 55.2±9.1 years) with $HER2^+$ breast cancer was included in the present study. Among them, 15 (30.6%) patients were premenopausal and the other 34 (69.4%) patients were postmenopausal (Table I). The mean tumor size was 5.0±1.2 cm. With regard to the TNM stage, 28 (57.1%) patients were assessed as stage IIB whereas the remaining 21 (42.9%) patients were assessed as stage IIIA. In addition, 26 (53.1%) patients received pyrotinib plus chemotherapy, while 23 (46.9%) patients were treated with pyrotinib plus trastuzumab and chemotherapy. The detailed baseline characteristics are shown in Table I. Moreover, the IHC examples in the breast tumor tissue of patients with Ki-67 level <30 or ≥30%, IHC++ and IHC+++ are shown in Fig. S1.

Clinical response following different therapy cycles. After a 2-cycle treatment, 23 (46.9%) and 26 (53.1%) patients achieved PR and SD, while no patient was assessed as CR or PD; the

Table I. Baseline characteristics of HER2$^+$ breast cancer patients.

Characteristics	Patients (n=49)
Mean age ± SD, years	55.2±9.1
Menopausal status, n (%)	
Premenopausal	15 (30.6)
Postmenopausal	34 (69.4)
ECOG PS, n (%)	
0	41 (83.7)
1	8 (16.3)
Mean tumor size ± SD, cm	5.0±1.2
Tumor stage, n (%)	
2	32 (65.3)
3	17 (34.7)
Node stage, n (%)	
1	35 (71.4)
2	14 (28.6)
Metastasis stage, n (%)	
0	49 (100.0)
Detailed TNM stage, n (%)	
T2N1M0	28 (57.1)
T2N2M0	4 (8.2)
T3N1M0	7 (14.3)
T3N2M0	10 (20.4)
TNM stage, n (%)	
IIB	28 (57.1)
IIIA	21 (42.9)
HER2 status, n (%)	
IHC++ and amplification via fluorescence *in situ* hybridization	11 (22.4)
IHC+++	38 (77.6)
Estrogen and/or progesterone receptor-positive, n (%)	31 (63.3)
Ki-67 level	
Mean ± SD, %	40.8±16.1
≥30%, n (%)	32 (65.3)
Therapy regimens, n (%)	
Pyrotinib plus chemotherapy	26 (53.1)
Pyrotinib plus trastuzumab and chemotherapy	23 (46.9)

SD, standard deviation; ECOG PS, eastern cooperative oncology group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

ORR and DCR were 46.9 and 100.0%, accordingly. Following a 4-cycle treatment, 2 (4.1%), 29 (59.2%) and 18 (36.7%) patients achieved CR, PR and SD, respectively, while none of patients underwent PD; moreover, the ORR and DCR were 63.3 and 100.0%, respectively. Following a 6-cycle treatment, 4 (8.2%), 36 (73.4%) and 9 (18.4%) patients achieved CR, PR and SD, respectively, and none of the patients exhibited PD; the ORR and DCR reached 81.6 and 100.0%, respectively (Table II).

Pathological response. After the neoadjuvant treatment, 23 (46.9%), 12 (24.5%), 12 (24.5%) and 2 (4.1%) patients were evaluated as MP grade 5, 4, 3 and 2, respectively. In addition, 23 (46.9%) and 40 (81.6%) patients achieved pCR in the breast tissue and the lymph nodes, respectively. Consequently, a total of 22 (44.9%) patients obtained tpCR (Table III). In addition, pyrotinib plus trastuzumab and chemotherapy (compared with that in the pyrotinib plus chemotherapy group) resulted in a higher tpCR rate in patients with HER2$^+$ breast cancer (65.2 vs. 26.9%; P=0.007; Fig. S2).

Prognostic factors. Higher T stage odds ratio (OR) (OR, 0.239 95% CI, 0.064-0.896; P=0.034) was related to declined tpCR; by contrast, IHC+++ (vs. IHC++ and gene amplification via FISH; OR, 12.353; 95% CI, 1.435-106.344; P=0.022) and pyrotinib plus trastuzumab and chemotherapy (vs. pyrotinib plus chemotherapy; OR, 5.089; 95% CI, 1.503-17.230; P=0.009) were both associated with elevated tpCR in patients with breast cancer (Fig. 1).

Moreover, subsequent multivariate logistic regression analysis demonstrated that pyrotinib plus trastuzumab and chemotherapy (vs. pyrotinib plus chemotherapy) was independently correlated with increased tpCR (OR, 3.977; 95% CI, 1.010-15.658; P=0.048). By contrast, higher Tumor (T) stage (OR, 0.226; 95% CI, 0.051-1.002; P=0.050) and IHC+++ (vs. IHC++ and gene amplification by FISH; O, 8.453; 95% CI, 0.879-81.315; P=0.065) only showed a trend (without statistical significance) of independently link with tpCR.

Adverse events. Generally, the majority of adverse events of pyrotinib-neoadjuvant therapy were mild and controllable (Table IV). The most frequent adverse events included diarrhea (81.6%), anemia (69.4%), nausea and vomiting (63.3%), and fatigue (51.0%). In addition, the grade 3 adverse events included diarrhea (16.3%), anemia (12.3%), nausea and vomiting (6.1%), fatigue (4.1%), thrombocytopenia (4.1%), leukopenia (2.0%), hypomagnesemia (2.0%), elevated transaminase (2.0%) and neutropenia (2.0%). No treatment-related death was reported.

Discussion

Recently, a small minority of studies supported the treatment efficacy of pyrotinib-neoadjuvant therapy in patients with HER2$^+$ breast cancer (18,22). For example, a recent study demonstrated that tpCR was 55.1% in patients with HER2$^+$ breast cancer who receive neoadjuvant pyrotinib plus docetaxel, carboplatin and trastuzumab treatment (18). An additional study indicated that following treatment with neoadjuvant pyrotinib plus albumin-bound paclitaxel, ORR and tpCR reached 100.0 and 57.1%, respectively, in patients with HER2$^+$ breast cancer (22). Similarly, the current study demonstrated that ORR and DCR reached 81.6 and 100.0%, respectively, following treatment with 6-cycle pyrotinib-neoadjuvant therapy in patients with HER2$^+$ breast cancer; moreover, 46.9 and 81.6% of patients achieved pCR in the breast tissue and in the lymph nodes, respectively, while 44.9% achieved tpCR. The findings of the present study, together with those reported in previous studies, implied the successful efficacy of pyrotinib-neoadjuvant therapy in treating patients with HER2$^+$ breast cancer. The possible explanations are listed as

Table II. Clinical response after 2, 4, and 6-cycle therapy in HER2$^+$ breast cancer patients.

Items	After 2-cycle	After 4-cycle	After 6-cycle
Clinical response by response evaluation criteria in solid tumors, n (%)			
Complete response	0 (0.0)	2 (4.1)	4 (8.2)
Partial response	23 (46.9)	29 (59.2)	36 (73.4)
Stable disease	26 (53.1)	18 (36.7)	9 (18.4)
Progressive disease	0 (0.0)	0 (0.0)	0 (0.0)
Objective response rate, n (%)	23 (46.9)	31 (63.3)	40 (81.6)
Disease control rate, n (%)	49 (100.0)	49 (100.0)	49 (100.0)

Table III. Pathological response in HER2$^+$ breast cancer patients who received pyrotinib-involved neoadjuvant therapy.

Items	n (%)
Miller-Payne grade	
Grade 5	23 (46.9)
Grade 4	12 (24.5)
Grade 3	12 (24.5)
Grade 2	2 (4.1)
pCR in breast	
Yes	23 (46.9)
No	26 (53.1)
Pathological complete response in lymph nodes	
Yes	40 (81.6)
No	9 (18.4)
Total pathological complete response	
Yes	22 (44.9)
No	27 (55.1)

follows: i) Pyrotinib could durably restrain tumor development by irreversibly inhibiting HER protein family homologous or heterodimer formation and their auto-phosphorylation (12,23); ii) a synergistic effect could be present between pyrotinib and chemotherapy, whose combination achieved improved treatment efficacy (24). Consequently, pyrotinib-neoadjuvant therapy possessed optimal treatment efficacy in patients with HER2$^+$ breast cancer. In addition, although the therapeutic regimen of the present study was similar to that used in previous studies (17,18), one of the previous studies was a phase II trial, which could not be extrapolated to the setting of clinical practice (18), while the other study had a relatively small sample size despite being a retrospective study (17). Consequently, the present study aimed to evaluate the efficacy and safety of pyrotinib-neoadjuvant therapy in a clinical population with a larger sample size.

With regard to the prognostic factors of patients with HER2$^+$ breast cancer, the present study demonstrated that pyrotinib plus trastuzumab and chemotherapy (vs. pyrotinib plus chemotherapy) was independently correlated with increased tpCR, which could be explained by the following points: Dual-HER2 targeted treatment was shown to result in a stronger antitumor effect; therefore, neoadjuvant pyrotinib plus trastuzumab and chemotherapy (vs. pyrotinib plus chemotherapy) was independently correlated with elevated tpCR in patients with HER2$^+$ breast cancer (25,26). In addition, higher T stage and IHC+++ (vs. IHC++ and amplification via FISH) could also predict tpCR to some degree. The possible reason is the following: i) Higher T stage, which represented larger tumor volume, resulting in enhanced invasiveness and tumor malignancy; therefore, patients with HER2$^+$ breast cancer and higher T stage could not readily achieve tpCR following pyrotinib-neoadjuvant treatment; ii) HER2 protein levels were elevated in patients classified as IHC+++ compared with those noted in patients classified as IHC++ and those who exhibited HER2 gene amplification via FISH; moreover, patients with higher HER2 protein levels demonstrated improved treatment response (27). Therefore, IHC+++ (vs. IHC++ and gene amplification via FISH) was associated with elevated tpCR.

Previous studies showed that the most common adverse events of pyrotinib-neoadjuvant therapy include diarrhea, dental ulcer, leukopenia and hand-foot syndrome (16,17,28,29). Consistent with the aforementioned studies, the present study identified that the majority of these adverse events involved in pyrotinib-neoadjuvant therapy were tolerable and controllable and included mild or moderate diarrhea (81.6%), anemia (69.4%), nausea and vomiting (63.3%). These findings supported the acceptable toxicity profile of pyrotinib-neoadjuvant therapy in treating patients with HER2$^+$ breast cancer. Furthermore, diarrhea was the most common side effect of pyrotinib and the possible reason could be the following: Pyrotinib inhibited the downstream signals of the epidermal growth factor receptor in the intestinal epithelium, which led to the activation of the basolateral membrane potassium channel and chloride secretory diarrhea (30,31).

Certain inevitable limitations existed in the present study. Firstly, this was a single-arm study, while randomized controlled trials would be necessary to compare the efficacy and safety between pyrotinib and other HER2-targeted agents used as neoadjuvant therapy in treating patients with HER2$^+$ breast cancer. Secondly, pyrotinib was developed very recently and the general survival of patients with breast cancer was relatively long; therefore, the follow-up duration

Table IV. Adverse events of pyrotinib-involved neoadjuvant therapy[a].

Events, n (%)	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	40 (81.6)	14 (28.6)	18 (36.7)	8 (16.3)	0 (0.0)
Anemia	34 (69.4)	18 (36.7)	10 (20.4)	6 (12.3)	0 (0.0)
Nausea and vomiting	31 (63.3)	14 (28.6)	14 (28.6)	3 (6.1)	0 (0.0)
Fatigue	25 (51.0)	12 (24.5)	11 (22.4)	2 (4.1)	0 (0.0)
Thrombocytopenia	21 (42.8)	13 (26.5)	6 (12.2)	2 (4.1)	0 (0.0)
Leukopenia	19 (37.7)	10 (20.4)	8 (16.3)	1 (2.0)	0 (0.0)
Hypomagnesemia	18 (36.7)	10 (20.4)	7 (14.3)	1 (2.0)	0 (0.0)
Elevated transaminase	18 (36.7)	10 (20.4)	7 (14.3)	1 (2.0)	0 (0.0)
Pruritus	17 (34.6)	11 (22.4)	6 (12.2)	0 (0.0)	0 (0.0)
Neutropenia	15 (30.6)	9 (18.4)	5 (10.2)	1 (2.0)	0 (0.0)
Anorexia	14 (28.6)	7 (14.3)	7 (14.3)	0 (0.0)	0 (0.0)
Elevated creatinine	14 (28.6)	9 (18.4)	5 (10.2)	0 (0.0)	0 (0.0)
Hypokalemia	9 (18.4)	6 (12.2)	3 (6.1)	0 (0.0)	0 (0.0)
Hyponatremia	5 (10.2)	3 (6.1)	2 (4.1)	0 (0.0)	0 (0.0)
Oral ulceration	4 (8.2)	2 (4.1)	2 (4.1)	0 (0.0)	0 (0.0)

[a]Each patient was counted once for the highest grade of each event experienced.

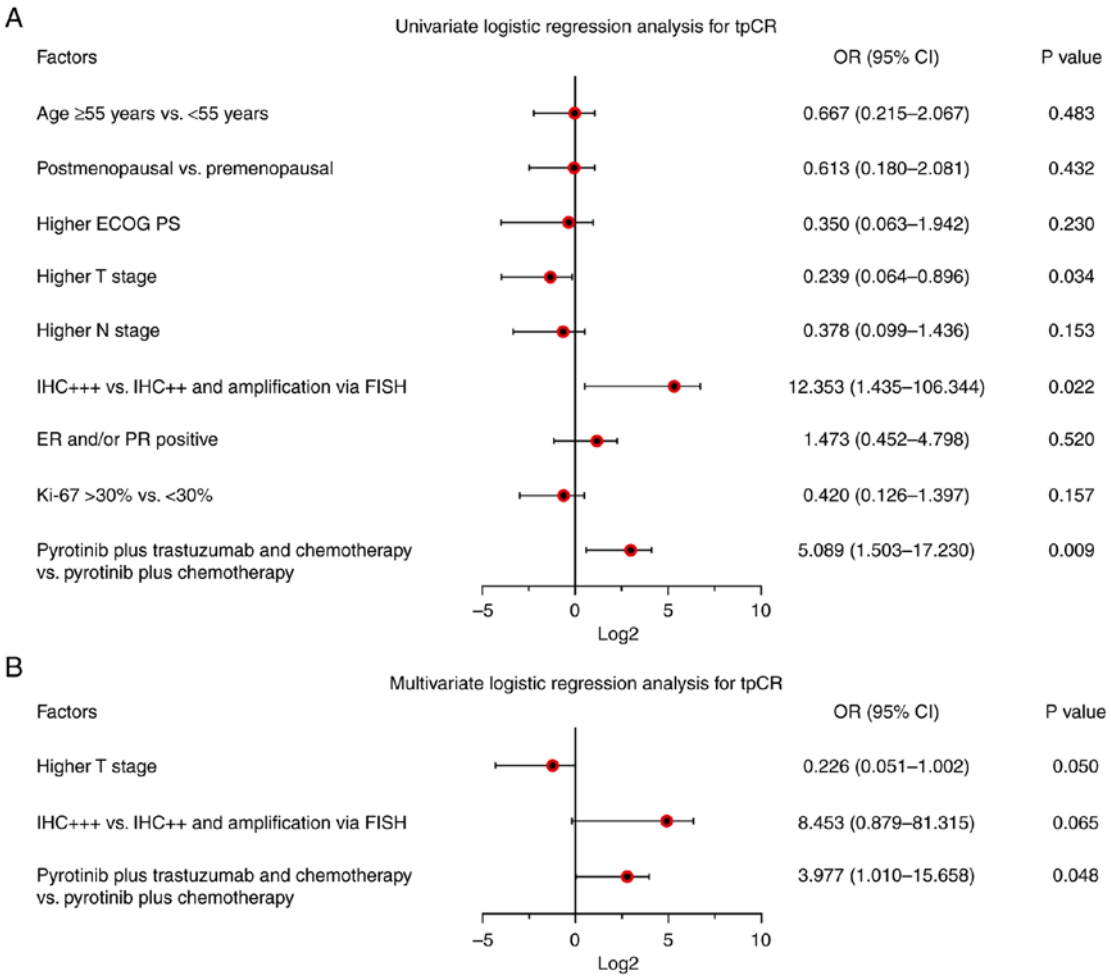

Figure 1. Influence factors of total pathological complete response in patients with breast cancer who received pyrotinib-involved neoadjuvant therapy. (A) Univariate and (B) Multivariate logistic regression analyses for prognostic factors of pyrotinib-involved neoadjuvant therapy in patients with human epidermal growth factor receptor 2-positive breast cancer. tpCR, total pathological complete response; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; OR, odds ratio; ER, estrogen receptor; PR, progesterone receptor; T, tumor; N, node; ECOG PS, eastern cooperative oncology group performance status.

period was not adequate for the objective evaluation of patient survival. Thirdly, the patients included in the present study were all Chinese and the treatment efficacy and safety of pyrotinib-neoadjuvant therapy should be evaluated in subsequent studies in populations comprising other ethnicities.

In summary, pyrotinib-neoadjuvant therapy achieved a tpCR of 44.9% and low incidence of grade 3-4 adverse events, indicating that pyrotinib-neoadjuvant therapy presented a relatively good efficacy and tolerance in treating patients with $HER2^+$ breast cancer. Nonetheless, the present findings warrant further large-scale studies for verification.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HW substantially contributed to the conception and design of the study. HC and ZG were responsible for the acquisition, analysis and interpretation of the data. All authors contributed to manuscript drafting and critical revisions of the intellectual content. HW and HC confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guangzhou Panyu Central Hospital (approval no. 2021-SR-512) in December 2021. All patients provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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