Original Article

# Neoadjuvant pyrotinib plus nab-paclitaxel, doxorubicin, and cyclophosphamide for HER2-positive locally advanced breast cancer: a retrospective case-series study

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**Background:** The anti-tumor activity of pyrotinib has been confirmed in human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. This study investigated the effect of pyrotinib plus nab-paclitaxel, doxorubicin, and cyclophosphamide as neoadjuvant therapy in patients with HER2-positive locally advanced breast cancer.

**Methods:** In this single-center retrospective study, female patients with HER2-positive locally advanced breast cancer received pyrotinib 320 mg orally once a day and the TAC regimen (nab-paclitaxel 260 mg/m$^2$, liposomal doxorubicin 20 mg/m$^2$, and cyclophosphamide 600 mg/m$^2$) on day 1 of each 21-day cycle. Surgery was performed after 4–6 cycles of neoadjuvant therapy. The outcomes included total pathological complete response (tpCR, ypT0/Tis ypN0) rate, objective response rate (ORR) after neoadjuvant therapy, progression-free survival, overall survival, and the incidence of adverse events (AEs).

**Results:** Between March 2019 and January 2020, a total of 22 patients were included. The median age was 48 years (range, 32–60). The ORR was 100% after the completion of neoadjuvant therapy. Ten (45.5%) patients achieved tpCR, including four of ten (40.0%) patients with positive hormone receptor, and six of 12 (50.0%) patients with negative hormone receptor. As at December 2020, no disease recurrence, progression, or death occurred. All patients suffered AEs after neoadjuvant therapy, most of which were grade 1–2. Grade ≥3 AEs included diarrhea [4 (18.2%)], rash [2 (9.1%)], and hand-foot syndrome [1 (4.5%)].

**Conclusions:** Neoadjuvant pyrotinib combined with the TAC regimen showed promising clinical benefit in patients with HER2-positive locally advanced breast cancer, with an acceptable safety profile.

**Keywords:** Pyrotinib; chemotherapy; neoadjuvant therapy; human epidermal growth factor receptor 2; breast cancer

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## Introduction

According to 2020 global estimates of the incidence and mortality for 36 cancers in 185 countries, female breast cancer has surpassed lung cancer as the leading cause of newly diagnosed cancer worldwide (1). The latest statistical report in China showed that the incidence of female breast cancer was 304,000 in 2015 (2). Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is an aggressive subtype, with higher risks of recurrence and metastasis, and worse prognosis (3,4). The use of anti-HER2 monoclonal antibody as (neo)adjuvant therapy has improved survival in patients with HER2-positive early or locally advanced breast cancer (5-10).

The current recommended neoadjuvant regimens in guidelines are chemotherapy combined with dual-targeted therapy (trastuzumab and pertuzumab) or mono-targeted therapy (trastuzumab) (11,12). However, some HER2-positive breast cancer patients, especially those with cardiovascular comorbidities, cannot use the large-molecule monoclonal antibody and anthracycline due to cardiac safety concerns. At the same time, new agents are emerging and their efficacy had been confirmed in metastatic and/or (neo)adjuvant settings. The phase 3 NeoALTTO trial demonstrated that dual inhibition of HER2 with lapatinib plus trastuzumab brought a significantly higher total pathological complete response (tpCR) rate than trastuzumab alone (46.8% *vs.* 27.6%), combined with paclitaxel in the neoadjuvant setting for HER2-positive early breast cancer (13). In the neoadjuvant phase 2 I-SPY 2 trial, the addition of neratinib to paclitaxel resulted in a higher tpCR rate than trastuzumab plus paclitaxel (39% *vs.* 23%) in patients with HER2-positive early breast cancer (14). The emergence of these small-molecule tyrosine kinase inhibitors (TKIs) provides more possible combinations for neoadjuvant HER2-directed therapy.

Pyrotinib is an irreversible pan-HER TKI targeting HER1, HER2, and HER4. Its anti-tumor activity has been confirmed in patients with previously treated, HER2-positive metastatic breast cancer (15-18), and was approved in China in 2018. There is no evidence showing that pyrotinib results in cardiotoxicity. Some phase 2 studies have investigated the application of neoadjuvant pyrotinib in patients with HER2-positive early or locally advanced breast cancer (19-21). Different neoadjuvant combinations were used in these studies to explore the optimal pyrotinib-based regimen. Herein, we investigated the effect of pyrotinib combined with a commonly used chemotherapy regimen (taxane/doxorubicin/cyclophosphamide) as neoadjuvant therapy in patients with HER2-positive locally advanced breast cancer. As the phase 3 GeparSepto-GBG 69 trial demonstrated that substituting the solvent-based paclitaxel with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) followed by epirubicin plus cyclophosphamide before surgery could significantly increase the tpCR rate (29.0% *vs.* 38.4%) in patients with early breast cancer (22), nab-paclitaxel was used in the present study. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/gs-21-770).

## Methods

### *Study population*

This was a retrospective case-series study of patients with HER2-positive locally advanced breast cancer who received neoadjuvant therapy with pyrotinib plus chemotherapy at Tangshan People's Hospital between March 2019 and January 2020. The eligibility criteria were as follows: (I) patients aged 18–75 years; (II) those with an Eastern Cooperative Oncology Group (ECOG) performance status 0–1; (III) treatment-naïve patients; (IV) those with pathologically confirmed HER2-positive (immunohistochemical score of 3+, or 2+ with fluorescence in situ hybridization positive) invasive breast cancer; (V) tumor >2 cm; (VI) patients with a known hormone receptor (HR) status; and (VII) those with complete treatment and follow-up data. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Ethics Committee of Tangshan People's Hospital (No. RMYY-LLKS-2021-063). Individual consent for this retrospective analysis was waived.

### *Treatment*

Poor tolerance to full dose of pyrotinib (400 mg once a day) due to high incidence of diarrhea was observed in clinical practice, leading to discontinuation of pyrotinib and inadequate treatment. Thus, these included patients in our center were treated with pyrotinib 320 mg orally once a day and the TAC regimen (nab-paclitaxel 260 mg/m$^2$, liposomal doxorubicin 20 mg/m$^2$, and cyclophosphamide 600 mg/m$^2$) on day 1 of each 21-day cycle. Surgery was performed after 4–6 cycles of neoadjuvant therapy. Adjuvant therapy was decided as per the doctor's discretion.

**Table 1** Baseline characteristics

| Characteristics | Patients (n=22) |
|---|---|
| Age (years), median [range] | 48 [32–60] |
| Medical history, n (%) | |
| Hypertension | 1 (4.5) |
| Diabetes mellitus | 1 (4.5) |
| Coronary heart disease | 2 (9.1) |
| T stage, n (%) | |
| T2 | 16 (72.7) |
| T3 | 6 (27.3) |
| N stage, n (%) | |
| N1 | 18 (81.8) |
| N2 | 4 (18.2) |
| Clinical stage, n (%) | |
| IIB | 7 (31.9) |
| IIIA | 15 (68.1) |
| ECOG performance status, n (%) | |
| 0 | 22 (100) |
| Hormone receptor status, n (%) | |
| ER and/or PgR positive | 10 (45.5) |
| ER and PgR negative | 12 (54.5) |
| Ki-67, n (%) | |
| <20% | 7 (31.8) |
| ≥20% | 15 (68.2) |

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor.

### *Data collection*

Demography, disease characteristics, treatment information, and follow-up data were collected from the patients' medical records. Resected tumor samples during surgery were used for pathological response assessment. Outpatient visit or telephone follow-up was censored in December 2020.

### *Outcomes*

The primary outcome was the tpCR (ypT0/Tis ypN0) rate, defined as the proportion of patients with an absence of invasive cancer components in the breast and without involvement of the axillary lymph nodes. Secondary outcomes included the objective response rate (ORR, defined as the proportion of patients with complete or partial response) after neoadjuvant therapy according to the Response Evaluation Criteria In Solid Tumors version 1.1, progression-free survival (PFS, defined as the time from surgery to disease progression or death from any cause), overall survival (OS, defined as the time from surgery to any-cause death), and the incidence of adverse events (AEs). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

### *Statistical analysis*

Descriptive statistics were used for data analysis. Continuous variables were expressed as the median (range), while categorical variables were expressed as a frequency (percentage). Histograms were used for the analysis of diarrhea.

## Results

A total of 22 patients with complete follow-up data were included for analysis. The median age of the patients was 48 years (range, 32–60). The predominant disease stage was T2 [16 (72.7%)] and N1 [18 (81.8%)]. All patients had an ECOG performance status of 0. Of the 22 patients, 10 (45.5%) showed positive estrogen receptor and/or positive progesterone receptor, while 12 (54.5%) exhibited a negative status of both HRs (*Table 1*).

A total of 16 (72.7%) patients received four cycles of neoadjuvant therapy, and six (27.3%) received six cycles. After the completion of neoadjuvant therapy, 12 (54.5%) patients achieved a complete response and 10 (45.5%) achieved a partial response, with an ORR of 100%. The tpCR rate was 45.5% (10/22) after surgery, including four of 10 (40.0%) patients with positive HR and six of 12 (50.0%) patients with negative HR. By the data cutoff date in December 2020, the median follow-up duration after surgery was 12.5 months (range, 6–20), and no disease recurrence, progression, or death occurred. The 6-month PFS and OS rates were both 100%.

All 22 (100%) patients suffered AEs after neoadjuvant therapy, the majority of which were grade 1–2. The most common (occurring in ≥20% patients) AEs were diarrhea [21 (95.5%)], hand-foot syndrome [21 (95.5%)], loss of appetite [17 (77.3%)], rash [12 (54.5%)], and asthenia [6 (27.3%)].

**Table 2** Adverse events after neoadjuvant therapy

| Events | Patients (n=22) | |
|---|---|---|
| | Any grade, n (%) | Grade ≥3, n (%) |
| Diarrhea | 21 (95.5) | 4 (18.2) |
| Hand-foot syndrome | 21 (95.5) | 1 (4.5) |
| Loss of appetite | 17 (77.3) | 0 |
| Rash | 12 (54.5) | 2 (9.1) |
| Asthenia | 6 (27.3) | 0 |
| ALT/AST increased | 3 (13.6) | 0 |
| Platelet count decreased | 3 (13.6) | 0 |
| Insomnia | 3 (13.6) | 0 |
| Creatinine increased | 2 (9.1) | 0 |
| Nausea/vomiting | 2 (9.1) | 0 |
| Triglycerides increased | 2 (9.1) | 0 |
| Weight loss | 2 (9.1) | 0 |
| Cardiotoxicity | 1 (4.5) | 0 |

ALT, alanine transaminase; AST, aspartate transaminase.

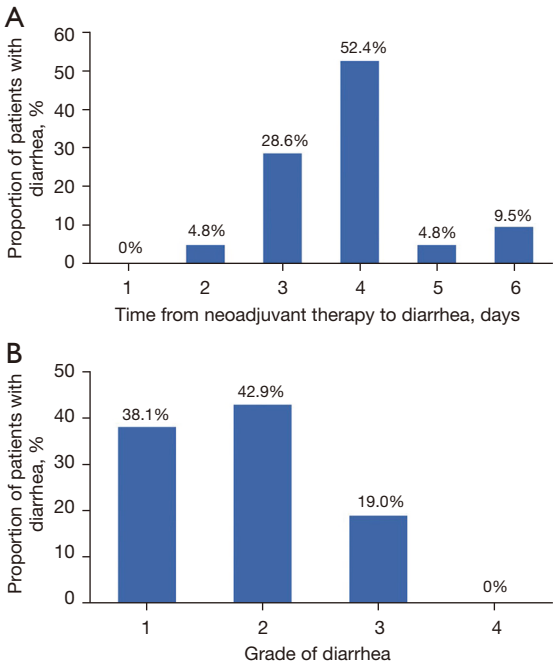


**Figure 1** Analysis of diarrhea. (A) Time from the initiation of neoadjuvant therapy to the occurrence of diarrhea. (B) Grade of diarrhea according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Grade ≥3 AEs included diarrhea [4 (18.2%)], rash [2 (9.1%)], and hand-foot syndrome [1 (4.5%)] (*Table 2*). Only one (4.5%) patient had a cardiotoxicity event, which was grade 1.

Of the 21 patients with diarrhea, the first event occurred at 2–6 days after the initiation of neoadjuvant therapy, and 11 (52.4%) patients suffered diarrhea at day 4 (*Figure 1A*). Grade 3 diarrhea occurred in four patients who recovered to grade 2 or below, and no grade 4 diarrhea was observed (*Figure 1B*).

## Discussion

This retrospective study investigated the effect of neoadjuvant pyrotinib combined with the TAC regimen (nab-paclitaxel/doxorubicin/cyclophosphamide) in patients with HER2-positive locally advanced breast cancer. The results showed that the ORR before surgery was 100% and the tpCR rate was 45.5%. This neoadjuvant regimen was also well-tolerated.

Previous randomized controlled trials (NeoALTTO, NeoSphere, and PEONY) showed that mono-targeted therapy with trastuzumab in combination with taxanes provided modest benefit on pathological response, with an tpCR rate of 21.5–27.6% (8,13,20). Taxanes combined with dual-targeted therapy with trastuzumab plus pertuzumab or lapatinib could increase the tpCR rate to 39.3–46.8% (8,13,23). The randomized phase 3 KRISTINE trial evaluated a new neoadjuvant strategy with antibody-drug conjugate trastuzumab emtansine plus pertuzumab without traditional chemotherapy, and the tpCR rate was 44.4% (24). The effect of pan-HER TKI pyrotinib combined with chemotherapy on pathological response seemed to be comparable to the aforementioned dual-targeted therapy with or without chemotherapy. However, the tpCR rate in the present study was lower than that with trastuzumab plus pertuzumab and chemotherapy (45.5% *vs.* 55.7–68.0%) in the KRISTINE study and randomized phase 3 TRAIN-2 trial (24,25), which might be due to the addition of carboplatin in both studies and the long treatment cycles (nine cycles) in the TRAIN-2 study. The majority (72.7%) of patients in the present study only received four cycles of neoadjuvant therapy. Despite the different clinical settings between the studies, the role of pyrotinib as a part of neoadjuvant therapy in HER2-positive breast cancer is worthy of further investigation.

The randomized phase 3 PHOEBE and PHENIX trials have confirmed the significant clinical benefit of pyrotinib

in HER2-positive metastatic breast cancer (16,17). In the neoadjuvant setting, data from three single-arm clinical trials in patients with HER2-positive early or locally advanced breast cancer have been reported. Liu *et al.* conducted a two-stage phase 2 trial of neoadjuvant pyrotinib plus docetaxel, carboplatin, and trastuzumab, and the first stage results showed that the tpCR rate was 51.6% (16/31) (19). Another two phase 2 trials showed that the tpCR rate was 57.1% (12/21) with pyrotinib plus nab-paclitaxel and trastuzumab (20), and 73.7% (14/19) with pyrotinib plus epirubicin and cyclophosphamide followed by pyrotinib plus docetaxel and trastuzumab (21). Combined with the results of the present study, pyrotinib-based neoadjuvant therapy provides a promising clinical benefit for patients with HER2-positive breast cancer. In addition, it should be noted that the present study was the only one investigating pyrotinib-based neoadjuvant therapy without trastuzumab or pertuzumab. This combination (pyrotinib plus nab-paclitaxel, doxorubicin, and cyclophosphamide) might be an alternative option for patients who could not receive large-molecule monoclonal antibody treatment. Given that the retrospective nature of the present study limited the reliability of results and different combinations were applied among the studies, the efficacy of pyrotinib-based neoadjuvant chemotherapy and the optimal combination need to be verified in large-scale clinical trials.

Small-molecule TKI pyrotinib can be taken orally without concern of cardiotoxicity, but pyrotinib-related diarrhea needs attention. The overall toxicity profile in the present study was acceptable. Diarrhea was the most frequent AE, with an incidence of 95.5%. The first diarrhea event occurred within 6 days after the initiation of neoadjuvant therapy and 52.4% of patients suffered diarrhea at day 4. The time to the first episode of diarrhea was early, which was consistent with previous reports in HER2-positive metastatic breast cancer (15-17). The incidence of grade 3 diarrhea in the present study was lower than previously reported results (18.2% *vs.* 28.6–64.5%) from phase 2 studies of pyrotinib-based neoadjuvant therapy (19-21). The dosage at 320 mg rather than 400 mg, the use of a single HER2-targeted agent, and no use of carboplatin might have contributed to the low incidence of grade 3 diarrhea. Diarrhea was reversible with anti-diarrhea treatment. In addition, since each patient received prophylactic treatment to increase the white blood cell count, no leukopenia occurred in the present study. A mild cardiotoxicity event was observed in one patient.

There were some limitations in this study that should be noted. Firstly, bias could not be avoided due to the retrospective nature and single-center design. Secondly, the sample size was relatively small. Finally, no control group was applied for direct comparison. Nevertheless, we aimed to provide more evidence on pyrotinib-based neoadjuvant therapy in HER2-positive breast cancer for subsequent clinical trials.

In conclusion, neoadjuvant pyrotinib combined with the TAC regimen (nab-paclitaxel/doxorubicin/cyclophosphamide) showed promising clinical benefit in patients with HER2-positive locally advanced breast cancer, with an acceptable safety profile. Large-molecule monoclonal antibody combined with small-molecule TKI and chemotherapy with different mechanisms of action maybe the mainstay treatment for HER-positive breast cancer in the near future. This combination in our study still warrants further investigation to provide an alternative option for patients who cannot receive large-molecule monoclonal antibody treatment.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/gs-21-770

*Data Sharing Statement:* Available at https://dx.doi.org/10.21037/gs-21-770

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/gs-21-770).

*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. All procedures performed in this study involving human participants were 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-2021-063). Individual consent for this retrospective analysis was waived.



 

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