Original Article

The efficacy and safety of trastuzumab and albumin-bound paclitaxel with or without pyrotinib as neoadjuvant therapy for HER2-positive breast cancer: a prospective observational cohort study

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Background: In the past few years, the combination of trastuzumab and paclitaxel has become an important option for human epidermal growth factor receptor-2 (HER2)-positive breast cancer. Small molecule tyrosine kinase inhibitors (TKIs) can bring clinical benefit to HER2-positive breast cancer patients. However, the efficacy and safety of these two regimens have not been compared. This study explored the efficacy and safety of pyrotinib combined with trastuzumab and albumin-bound paclitaxel (nab-paclitaxel).

Methods: Patients with newly diagnosed HER2-positive early or locally advanced breast cancer treated at The Tumor Hospital of Mudanjiang City from November 2020 to June 2022 were included. The control group received pertuzumab in combination with nab-paclitaxel, whereas the pyrotinib group received pyrotinib in combination with pertuzumab and nab-paclitaxel as treatment, in a 3-week cycle for 4 cycles. The primary endpoints of this study were total pathological complete response (tpCR) rate, breast pathological complete response (bpCR) rate, and the secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and the occurrence of adverse events (AEs).

Results: A total of 72 patients were enrolled in the study and completed the study treatment. Baseline characteristics were well balanced between these two arms. In the control group, the tPCR rate was 23.68%, and the bpCR rate was 47.36%. In the pyrotinib group, the tPCR rate was 47.06%, and the bpCR rate was 64.71%. The tPCR rate in the pyrotinib group was significantly higher than that in the control group (P=0.049). The ORR in the pyrotinib group (67.65%) was significantly higher than that in the control group (42.11%, P=0.04). The median PFS (mPFS) for the control group was 9.24 months, with a mean PFS of 10.01±0.44 months [95% confidence interval (CI): 9.14–10.88 months]. In the pyrotinib group, mPFS was 9.74 months, with a mean PFS of 11.25±0.29 months (95% CI: 10.67–11.82 months). The PFS in the pyrotinib group was significantly longer than that in the control group (P=0.045). Safety results showed that the overall incidence of AEs in the control group was 68.42%, with a 3-grade adverse reaction rate of 21.05%. In the pyrotinib group, the overall incidence of AEs was 79.41%, with a 3-grade adverse reaction rate of 29.41%. The difference between the two groups was not statistically significant (P>0.05).

Conclusions: Pyrotinib group in neoadjuvant treatment for HER2 positive breast cancer has obvious

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short-term efficacy advantages over control group. This treatment regimen can prolong PFS for 1 year, and the safety during medication is controllable. This study still has some limitations, with the relatively small sample size and relatively short follow-up period, and a further large-scale, multicenter, randomized controlled trial is necessary to verify the clinical value of this dual-target treatment regimen.

Keywords: Pyrotinib; pertuzumab; neoadjuvant therapy; human epidermal growth factor receptor-2 (HER2); breast cancer

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Introduction

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is a distinct subtype of breast cancer, accounting for approximately 20–25% of all breast cancers. This subtype is characterized by its aggressive nature and is often associated with a poorer prognosis and a higher rate of recurrence (1,2). For patients with HER2-positive breast cancer who are eligible for surgery, neoadjuvant anti-HER2 therapy has become a standard treatment strategy. The achievement of pathological complete response (pCR) after neoadjuvant treatment is a well-recognized surrogate endpoint for long-term event-free survival and overall survival (OS) outcomes (3).

Although neoadjuvant therapy such as chemotherapy and targeted therapy has made some progress in the treatment of HER2-positive breast cancer and the combination between different drugs has been shown to improve the pCR rate of HER2-positive breast cancer, not all HER2-positive breast cancer patients are sensitive to trastuzumab treatment. Primary resistance or secondary resistance may occur after trastuzumab, eventually leading to poor neoadjuvant therapy outcomes. In the NeoSphere and PEONY studies, wherein HER2-positive breast cancer received pertuzumab combined with trastuzumab and docetaxel, the total pathological complete response (tpCR) rate was only 39.3%. Recently, with the continuous development of targeted therapy, pyrotinib-based targeted therapeutic drugs have been widely used in the treatment of HER2-positive breast cancer (4,5). Pyrotinib is an irreversible small-molecule tyrosine kinase inhibitor (TKI) developed in China that targets HER2 and epidermal growth factor receptor (EGFR). The PHEDRA study demonstrated that pyrotinib combined with trastuzumab and docetaxel effectively increased the tpCR rate of 41.0% in HER2-positive breast cancer in the pyrotinib group and by 22% in the placebo group; the objective response rate (ORR) was 91.6% and 81.6% in pyrotinib group and placebo group, respectively. This experimental study provides a new therapeutic option for HER2-positive breast cancer patients (6). From the perspective of adverse reaction events, the incidence of diarrhea in pyrotinib group was higher than that in placebo group, but most of

Highlight box

Key findings

- Giving pyrotinib plus trastuzumab with albumin paclitaxel neoadjuvant treatment for human epidermal growth factor receptor 2 (HER2) positive breast cancer.

What is known and what is new?

- Pyrotinib can completely block the downstream pathway of homologous and heterodimers of HER family, and may still be effective in patients with trastuzumab-resistant drugs. Based on the results of previous phase, PHOEBE study and PHENIX study data, the usefulness of pyrotinib in the treatment of patients with HER2 positive advanced breast cancer was recognized.
- Recent studies investigating this multitargeted treatment regimen can further improve survival and pathological response. The purpose of this study is to investigate the clinical efficacy and safety of neoadjuvant therapy of pyrotinib combined with trastuzumab and albumin paclitaxel in patients with HER2 positive breast cancer, with a view to providing new therapeutic strategies for clinical practice to further improve patient survival.

What is the implication, and what should change now?

- This study demonstrated significant short- and long-term advantages of combining pyrotinib together with trastuzumab with neoadjuvant albumin paclitaxel in the treatment of HER2-positive breast cancer, but this study still has some limitations, with the relatively small sample size and relatively short follow-up period, and a further large-scale, multicenter, randomized controlled trial is necessary to verify the clinical value of this dual-target treatment regimen.

them were grade 1–2 diarrhea, and the overall safety was controllable (6). Pertuzumab, a humanized monoclonal antibody, binds to the HER2 molecules on the surface of HER2-positive tumor cells, inhibiting tumor cell growth and metastasis (7). Additionally, albumin-bound paclitaxel (nab-paclitaxel) is a novel microtubule-stabilizing agent with lower toxicity and better drug delivery properties, compared to other purple shirt drugs, offering new hope for the treatment of HER2-positive breast cancer patients.

In recent years, the combination of trastuzumab and paclitaxel has become an important treatment option for HER2-positive breast cancer, significantly improving disease-free survival and OS rates (8). A recent study has further explored the combination of trastuzumab and paclitaxel with other HER2-targeted therapies, such as lapatinib, and has found that this multi-targeted treatment approach can further enhance survival and pathological response rates (9). Furthermore, several previously studies have demonstrated the efficacy and safety profile of pyrotinib in combination with nab-paclitaxel in patients with HER2-positive breast cancer (10-12). However, the clinical benefit of pyrotinib in combination with pertuzumab and albumin-bound paclitaxel has not been investigated.

In this study, we investigated the clinical efficacy and safety of pyrotinib in combination with pertuzumab and nab-paclitaxel as neoadjuvant therapy in patients with HER2-positive breast cancer. We aimed to provide new treatment strategies for clinical practice to improve patient survival. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-81/rc).

Methods

Clinical data

In this prospective observational cohort study, HER2-positive early or locally advanced female breast cancer patients admitted to The Tumor Hospital of Mudanjiang City from November 2020 to June 2022 were included. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The Tumor Hospital of Mudanjiang City (No. 2020-02-01). Individual consent for this retrospective analysis was waived. The inclusion criteria were as follows: (I) age >18 years; (II) exclusion of distant metastasis before neoadjuvant therapy, according to the 8th edition of the American Joint Committee on Cancer (AJCC) breast cancer tumor-node-metastasis (TNM) staging, stages II–III (13); (III) presence of at least 1 measurable target lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; (IV) histopathological confirmation of invasive breast cancer with immunohistochemical staining of HER2 as 3+ or 2+ and *HER2* gene amplification confirmed by fluorescence in situ hybridization (FISH); (V) Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1. The exclusion criteria were as follows: (I) incomplete clinical data; (II) inability to swallow, chronic diarrhea, intestinal obstruction, or other conditions affecting drug administration and absorption; (III) inflammatory breast cancer, bilateral breast cancer; (IV) pregnant and lactating women; (V) patients who received less than 4 cycles of targeted therapy during neoadjuvant treatment.

Treatment regimen

The control group (pertuzumab in combination with nab-paclitaxel): nab-paclitaxel (Shiyao Group Ouyi Pharmaceutical Co., Ltd., Shijiazhuang, China) was administered at a dose of 260 mg/m^2 via intravenous infusion over 30 minutes on day 1 of each 21-day cycle for a total of 4 cycles. Pertuzumab (Roche Pharmaceuticals Ltd., Shanghai, China) was administered as follows: an initial loading dose of 8 mg/kg was administered as a 90-minute intravenous infusion on day 1 of the first cycle, followed by a maintenance dose of 6 mg/kg given as a 60-minute intravenous infusion on day 1 of subsequent cycles, each lasting 21 days, for a total of 4 cycles.

Pyrotinib group (pyrotinib in combination with pertuzumab and nab-paclitaxel neoadjuvant therapy): in addition to the treatment received by the control group, patients in the pyrotinib group received oral pyrotinib at a dose of 400 mg once daily on the first day of each treatment cycle. For patients who experienced severe diarrhea, the dose of pyrotinib was reduced to 320 mg once daily.

Both groups received supportive care including hydration, antiemetics, gastrointestinal protection, and hepatic protection during the treatment period. Before each cycle of neoadjuvant chemotherapy, patients underwent routine laboratory tests, including complete blood count, liver and kidney function, and electrolytes. If significant abnormalities in these indicators occurred, appropriate measures were taken, and chemotherapy was administered according to the established protocol once the indicators

allowed. Surgery was performed within 14 days after completing 4 cycles of treatment. Targeted therapy was continued for at least 1 year according to the pathological results and guidelines. The clinical data for these patients were prospectively collected via electronic medical record data. Patients were followed up every 3 months after surgery until 5 years had elapsed or disease progression occurred.

Clinical efficacy assessment and outcome measures

Primary outcome measures

Pathological response assessment: according to the commonly used Miller-Payne (MP) grading system in the domestic pathology field (14), we compared pre-treatment core needle biopsy specimens with post-operative specimens. This primarily assessed the cell richness of residual tumors in the breast primary lesion after neoadjuvant therapy and is graded on a scale from 1 to 5. A higher grade indicated fewer infiltrating cancer cells, with grade 5 indicating no infiltrating cancer cells in the original tumor bed but possible presence of ductal carcinoma *in situ*. When tissue pathology was classified as MP5 and regional lymph nodes showed no cancer cells (ypT0/is, ypN0), it was defined as tpCR; a simple MP5 classification was defined as pCR.

Secondary outcome measures

(I) Targeted therapy was continued for at least 1 year according to the pathological results and guidelines. Patients were followed up every 3 months after surgery for 5 years or until disease progression.

(II) ORR: patients underwent breast ultrasound, breast magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT) scans before treatment and after the completion of neoadjuvant therapy (before surgery). Patient objective response was assessed based on RECIST 1.1. ORR was calculated as the sum of complete response (CR) and partial response (PR).

(III) Adverse events (AEs): AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 by the National Cancer Institute.

Statistical analysis

Continuous variables were described as mean ± standard deviation and categorical variables as percentages. Statistical analysis was performed using the software SPSS 26.0 (IBM Corp., Armonk, NY, USA). Independent sample *t*-tests were used for normally distributed continuous data. Categorical data were compared between groups using Fisher's exact probability test. Survival analysis was conducted using the Kaplan-Meier method, and survival curves were plotted. The median progression-free survival (mPFS) was estimated. The efficacy and safety were evaluated in the intention-to-treat population. A 2-sided P value of <0.05 was considered statistically significant.

Results

Clinical and pathological characteristics of patients

A total of 86 patients with newly diagnosed HER2-positive early or locally advanced breast cancer were collected from The Tumor Hospital of Mudanjiang City between November 2020 and June 2022. According to the inclusion and exclusion criteria, 3 patients were excluded due to inadequate use of targeted drugs during neoadjuvant therapy, 4 patients were excluded due to distant metastasis before neoadjuvant therapy, 2 patients were excluded due to pregnancy, and 5 patients were excluded due to incomplete clinical data. Ultimately, 72 patients were included in the study.

Among them, there were 38 cases in the control group and 34 cases in the pyrotinib group. The specific clinical characteristics of the two groups of patients are shown in *Table 1*, and there were no statistically significant differences in all clinical characteristics between the groups (P>0.05).

Evaluation of the pathological efficacy of the two

In the control group, 9 patients (23.68%) achieved tPCR, and 18 patients (47.36%) achieved bpCR. In the pyrotinib group, 16 patients (47.06%) achieved tPCR, and 22 patients (64.71%) achieved bpCR. The tPCR rate in the pyrotinib group was significantly higher than that in the control group (P=0.049). Although the bpCR rate was higher in the pyrotinib group than in the control group, the difference between the two groups was not statistically significant (P=0.16) (*Figure 1*).

Comparison of ORR between the two groups

According to the RECIST 1.1 criteria (15), in the control group, 4 patients (10.53%) achieved CR, and 12 patients

Table 1 Comparison of the clinical characteristics of the two groups

Clinical characteristics	Control group (n=38)	Pyrotinib group (n=34)	P value
Age (years)	47.55±10.04	51.06±9.57	0.09
BMI (kg/m^2)	23.78±1.30	24.29±1.73	0.16
ECOG score			0.32
0	23	25	
1	15	9	
TNM stage			0.36
II	22	15	
III	16	19	
Pathological subtypes			0.31
Invasive ductal carcinoma	29	22	
Invasive lobular carcinoma	9	12	
Location			0.25
Left	17	20	
Right	21	14	
Hormone receptor status			0.47
ER and/or PR positive	25	19	
ER and PR negative	13	15	
Menopausal status			0.33
Yes	22	24	
No	16	10	

Data are presented as number or mean ± standard deviation. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; TNM, tumor-node-metastasis; ER, estrogen receptor; PR, progesterone receptor.

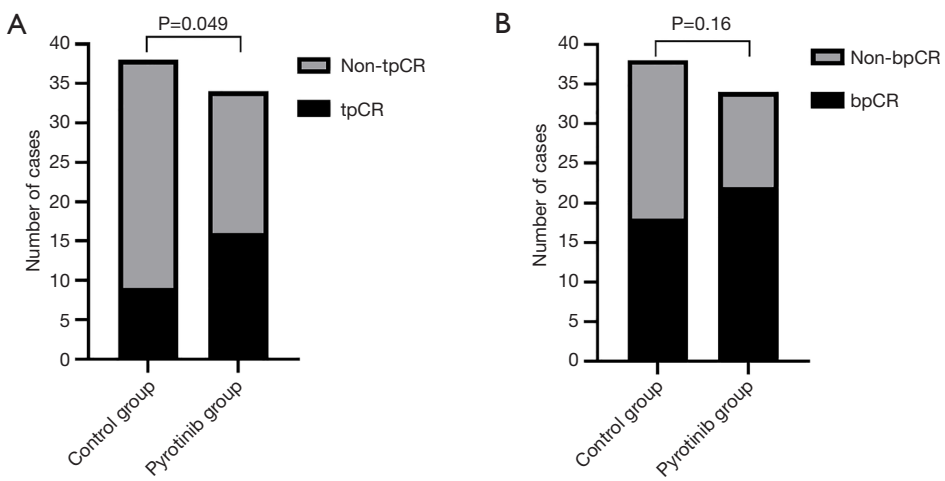

Figure 1 Assessment of pathological response in both groups. (A) Comparison of tPCR rates between the two groups; (B) comparison of bpCR rates between the two groups of patients. tPCR, total pathological complete response; bpCR, breast pathological complete response.

Table 2 Clinical responses following neoadjuvant treatment assessed by RECIST v1.1

Groups	Best overall response, n (%)					P value
	CR	PR	SD	PD	ORR	
Control group (n=38)	4 (10.53)	12 (31.58)	18 (47.37)	4 (10.53)	16 (42.11)	0.04
Pyrotinib group (n=34)	6 (17.65)	17 (50.00)	9 (26.47)	2 (5.88)	23 (67.65)	

CR: disappearance of all lesions and pathologic lymph nodes. PR: ≥30% decrease SLD; no new lesions; no progression of non-target lesions. SD: no PR-no PD. PD: ≥20% increase SLD compared to smallest SLD in study or progression of non-target lesions or new lesions. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; SLD, sum of the longest diameters.

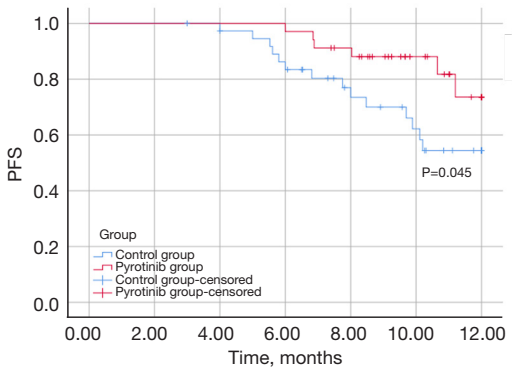

Figure 2 The 1-year PFS survival curves of the two groups of patients after neoadjuvant therapy. PFS, progression-free survival.

(31.58%) achieved PR, resulting in an ORR of 42.11%. In the pyrotinib group, 6 patients (17.65%) achieved CR, and 17 patients (50.00%) achieved PR, resulting in a significantly higher ORR of 67.65% compared to the control group (P=0.04) (*Table 2*).

Comparison of PFS between the two groups

As of June 2023, all patients had been followed up for 1 year to record disease progression. In the control group, the mPFS was 9.24 months, with a mean PFS of 10.01±0.44 months (95% CI: 9.14–10.88 months). In the pyrotinib group, the mPFS was 9.74 months, with a mean PFS of 11.25±0.29 months (95% CI: 10.67–11.82 months). There was a statistically significant difference in PFS survival between the two groups (P=0.045), indicating that the pyrotinib group had a significantly longer PFS compared to the control group (*Figure 2*).

Occurrence of AEs

In this study, the overall incidence of AEs in the control group was 68.42% (26/38), with a 3rd-grade AE incidence of 21.05% (8/38). There were no cases of drug-related AE-related deaths. The most common AE was diarrhea (52.63%), with a 3–4 grade diarrhea incidence of 15.79%. AEs led to treatment modification or discontinuation in 3 cases, whereas only dose reduction was required in 7 cases. In the pyrotinib group, the overall incidence of AEs was 79.41% (27/34), with a 3rd-grade AE incidence of 29.41% (10/34). There were no cases of drug-related AE-related deaths in this group either. The most common AE was diarrhea (67.65%), with a 3–4 grade diarrhea incidence of 23.53%. AEs led to treatment modification or discontinuation in 4 cases, whereas only dose reduction was required in 10 cases. There was no statistically significant difference in the overall incidence of AEs between the two groups (P=0.42) (*Table 3*).

Discussion

Previous studies have reported combination therapy of dual targeting and chemotherapy in HER2-positive breast cancer, achieving pCR rates ranging from 39% to 68%, and even reaching an astonishing pCR rate of over 90% in sub-studies of hormone receptor (HR)-negative/HER-2 positive populations, such as the WSG-ADAPT study (16). A review of the NOAH study (17) results indicated that adding pertuzumab to standard neoadjuvant chemotherapy could lead to more HER2-positive patients achieving pCR. However, some patients still exhibit no significant response to the drugs, and even develop resistance (18). In comparison to traditional antibody drugs

Table 3 Incidence of AEs during neoadjuvant therapy in the two groups

AEs	Control group (n=38)		Pyrotinib group (n=34)	
	All grades	3–4 grade	All grades	3–4 grade
Diarrhea	20 (52.63)	6 (15.79)	23 (67.65)	8 (23.53)
Anemia	15 (39.47)	5 (13.16)	13 (38.24)	7 (20.59)
Neutropenia	8 (21.05)	2 (5.26)	10 (29.41)	4 (11.76)
Rash	6 (15.79)	0	7 (20.59)	0
Elevated aspartate aminotransferase	13 (34.21)	1 (2.63)	11 (32.35)	0
Elevated alanine aminotransferase	11 (28.95)	0	12 (35.29)	1 (2.94)
Fatigue	16 (42.11)	0	18 (52.94)	0
Oral ulcer	4 (10.53)	0	4 (11.76)	0
Nausea	12 (31.58)	0	15 (44.12)	0

Data are presented as n (%). AEs, adverse events.

such as pertuzumab, pyrotinib has mechanistic advantages. Pertuzumab primarily acts on HER2-HER2 homodimers, with relatively weak blocking effects on ligand-induced HER2 heterodimer signaling pathways. In contrast, pyrotinib can comprehensively block downstream pathways of the HER family of homodimers and heterodimers. Moreover, due to differences in their mechanisms of action, pyrotinib may remain effective for patients who have developed resistance to pertuzumab. Based on the results of previous phase II studies, and the PHOEBE and PHENIX trials, pyrotinib in combination with capecitabine for HER2-positive metastatic breast cancer has shown an mPFS ranging from 11.1 to 18.1 months, with an impressive ORR of 67.2% to 78.5% (19-21). These data underscore the effectiveness of pyrotinib in the treatment of HER2-positive breast cancer patients. The aim of this study was to explore the clinical efficacy and safety of pyrotinib in combination with pertuzumab and nab-paclitaxel as neoadjuvant therapy for HER2-positive breast cancer.

Firstly, the author compared the pathological treatment responses of the two groups. tpCR is a comprehensive metric that includes an assessment of both breast tissue and lymph nodes. The pyrotinib group's tpCR rate was significantly higher than that of the control group, suggesting that the neoadjuvant therapy regimen involving pyrotinib in combination with pertuzumab and nab-paclitaxel is more effective at achieving a comprehensive eradication of HER2-positive breast cancer. This finding aligns with the effectiveness of pyrotinib and pertuzumab in HER2-positive breast cancer treatment observed in other studies (15,22). Although the pyrotinib group outperformed the control group in terms of bpCR, this difference did not reach statistical significance, possibly due to the limited sample size. Nevertheless, it is noteworthy that the bpCR rate remained relatively high in the pyrotinib group, implying the potential efficacy of this treatment regimen in breast tissue. In this study, the pyrotinib group not only excelled in achieving CR but also demonstrated an advantage in PR. The pyrotinib group ORR was 67.65%, significantly higher than that of the control group (42.11%), which was consistent with the data from the aforementioned studies (18-20). This finding further supports that the combination of pyrotinib with pertuzumab and nab-paclitaxel is an effective treatment regimen for HER2-positive breast cancer patients. High ORR is associated with favorable short-term outcomes, and in conjunction with the significant improvement in tpCR, this treatment regimen demonstrates potential advantages in both short-term and possibly long-term efficacy. To validate whether this dual-targeted treatment approach can translate into long-term survival benefits, the author conducted a 1-year follow-up for all patients, plotting patient PFS curves. The results showed that the pyrotinib group's PFS was significantly longer than that of the control group, indicating that pyrotinib in combination with pertuzumab and nab-paclitaxel can markedly enhance the long-term prognosis of HER2-positive breast cancer patients. This study also conducted a comparative analysis of AEs that occurred during the treatment period in both groups. Despite the pyrotinib group's advantage in terms of efficacy, the overall

incidence of AEs and the rate of grade 3 AEs were slightly higher compared to the control group. Particularly, diarrhea, as the most common AE, had a higher incidence in the pyrotinib group. These findings suggest that although this combination treatment regimen has potential advantages in terms of efficacy, it may also come with a higher risk of AEs. Patients in both the pyrotinib and control groups required treatment discontinuation or modification. This highlights the importance of closely monitoring patients' adverse reactions and promptly managing them when implementing this combination treatment regimen (23). It is important to note that this study has certain limitations, including a relatively small sample size and a relatively short follow-up period. Further large-scale, multicenter, randomized controlled trials are necessary to validate the clinical value of this dual-targeted treatment approach.

Conclusions

In summary, this study demonstrates that the neoadjuvant treatment of HER2-positive breast cancer with a combination of pyrotinib, trastuzumab, and albumin-bound paclitaxel offers significant short- and long-term advantages. However, it may also come with a higher risk of AEs. Therefore, when considering the use of this treatment regimen, a patient's individual circumstances should be carefully evaluated, weighing the benefits against the potential safety concerns.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-81/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-81/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-81/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-81/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 board of The Tumor Hospital of Mudanjiang City (No. 2020-02-01). Individual consent for this retrospective analysis was waived.

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