

Feasibility Study of Pyrrolitinib-Based Dual-Target Therapy for Neoadjuvant Treatment of HER2-Positive Breast Cancer Patients

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Background: HER2-positive breast cancer is one of the high-risk subtypes of breast cancer for which dual-targeted therapy has become an important treatment option. However, for some patients, complete control of the disease is still not possible and additional treatment is required. Pyrrolitinib, an inhibitor of ALK and MET, has shown promising efficacy in breast cancer treatment. The aim of this study was to investigate the feasibility of adjuvant intensive therapy with pyrrolitinib in the treatment of HER2-positive breast cancer tumors.

Materials and Methods: Twenty-eight patients with HER2-positive breast cancer who were treated at the Breast Surgery Department of the Provincial Hospital of Weihai City, Shandong Province, China, between January 1, 2019, and January 1, 2023, were selected for this study. All of these patients received dual-targeted therapy with the addition of pyrrolitinib therapy adjuvant intensive therapy. We recorded data on the patients' basic information, pathological characteristics, treatment regimens, effects of treatment regimens, and adverse reactions, and statistically analyzed them.

Results: Of the 28 patients with HER2-positive breast cancer, all of them were added to adjuvant intensive therapy with pyrrolitinib. After examination of the samples during treatment, the breast cancer mass had been significantly reduced with the assistance of pyrrolitinib. In addition, no serious adverse reactions were found.

Conclusion: Adjuvant intensification of pyrrolitinib in the treatment of HER2-positive breast cancer tumors is feasible. The results of this study suggest that pyrrolitinib is a safe and effective therapeutic option that can significantly improve the outcome of HER2-positive breast cancer. More studies are needed to further validate this finding.

Keywords: HER2-positive breast cancer, dual-target therapy, pyrrolitinib, adjuvant intensive therapy, feasibility study

Introduction

Breast cancer is recognized as a heterogeneous disease, with HER2-positive breast cancer constituting a particularly aggressive subtype characterized by the overexpression or amplification of the HER2 gene, which is associated with a poor prognosis and high risk of recurrence.^{1,2} The treatment landscape for HER2-positive breast cancer has evolved significantly, yet many patients remain unresponsive to traditional chemotherapeutic agents, underscoring the limitations of current treatment paradigms.³ Consequently, the advent of targeted HER2 therapy has revolutionized the therapeutic approach,⁴ with dual-targeted therapies emerging as an essential component in the management of this subtype.⁵

Recent advances in research have led to the exploration of various therapeutic strategies that encompass both monoclonal antibodies and small molecule inhibitors.⁶ Pyrrolitinib, a novel small molecule inhibitor, specifically targets both ALK and MET proteins, and has demonstrated potent antitumor activity in preclinical and clinical settings.⁷ Notably, clinical trials have established that pyrrolitinib monotherapy can achieve over 40% response rates in patients with HER2-positive advanced breast cancer.⁸ Furthermore, emerging data indicate that the integration of pyrrolitinib with existing therapeutic regimens enhances efficacy while also maintaining patient safety.⁹ For instance, studies by Xiu M et al¹⁰ have shown that Dose-dense

paclitaxel plus carboplatin in combination with trastuzumab leads to synergistic effects, significantly improving overall response rates compared to monotherapy.

Despite these promising findings, critical uncertainties remain regarding the feasibility of using pyrrolitinib in the neoadjuvant setting for early-stage HER2-positive breast cancer. Key considerations include the optimal dosing strategies and treatment regimens that would maximize therapeutic benefits while minimizing adverse effects. Comparative studies, such as those conducted by Pengnam S et al¹¹ have highlighted that dual-targeted approaches could potentially enhance pathologic complete response rates in early-stage HER2-positive patients compared to traditional neoadjuvant chemotherapy alone.

Therefore, the primary aim of this study is to evaluate the feasibility and efficacy of pyrrolitinib as an adjuvant therapy in patients with HER2-positive breast cancer. We will achieve this by retrospectively analyzing clinical data from 28 patients to assess safety, efficacy, and overall treatment outcomes. By situating our findings within the context of the existing literature and ongoing trials, we hope to elucidate the potential role of pyrrolitinib in expanding treatment options and improving survival quality for HER2-positive breast cancer patients. Ultimately, our analysis aims to contribute to a deeper understanding of pyrrolitinib's therapeutic implications and inform future clinical strategies.

Methodology

Materials and Methods

This is a retrospective clinical study. Twenty-eight patients with HER2-positive breast cancer treated at the Department of Breast Surgery of the Provincial Hospital of Weihai City, Shandong Province, China, who received pyrrolitinib additionally to dual-targeted therapy, were included in this study. Baseline information about the patients was collected from their medical records, including their age, pathologic type, lymph node metastasis, tumor stage, and prognostic factors. The patient's treatment regimen involved dual-targeted therapy and pyrrolitinib therapy for drug dosage and regimen exploration, and information on treatment efficacy, adverse reactions, and clinical outcomes were recorded during follow-up (Figure 1).

The efficacy and adverse effects of pyrrolitinib will be collected and analyzed by retrospectively analyzing the clinical records of the patients and compared with their health status and treatment regimen before treatment. Study data will be viewed using descriptive statistics and composite assessments to look at the efficacy, including safety and effectiveness, of pyrrolitinib in the treatment of HER2-positive breast cancer.

Inclusion and Exclusion Criteria

Inclusion Criteria: 1. Age \geq 18 years; all participants had no reported family history of breast cancer; 2. Patients diagnosed with early-stage or metastatic HER2-positive breast cancer who underwent surgical treatment; 3. All patients received standardized dual-targeted therapy, including trastuzumab and chemotherapy.

Participants underwent a minimum of six cycles of pyrrolitinib treatment; 4. All individuals underwent imaging examinations before and after treatment to assess therapeutic outcomes; 5. All participants provided informed consent to participate in this clinical study.

Exclusion Criteria: 1. Patients with malignant tumors that contraindicate neoadjuvant therapy, including advanced liver or lung failure, lymph node metastasis, or brain metastasis; 2. Individuals with a history of prior treatments, including surgery, chemotherapy, radiotherapy, or endocrine therapy; 3. Patients suffering from severe cardiac conditions or immune system disorders that may compromise the ability to achieve a safe and effective therapeutic outcome; 4. Participation in other clinical trials or previous treatment with pyrrolitinib before the current treatment regimen; 5. Patients with significant mental or neurological disorders that would impede their ability to adhere to the treatment protocol; 6. Individuals who decline to provide the necessary data for the study or refuse authorization for the use of relevant information.

Ethical Review

The study was approved by the Ethics Committee of the Provincial Hospital of Weihai City, Shandong Province, China, and was executed in accordance with the principles of the World Declaration on Medical Ethics and the Guiding Principles of Ethics, with all patients signing an informed consent form.

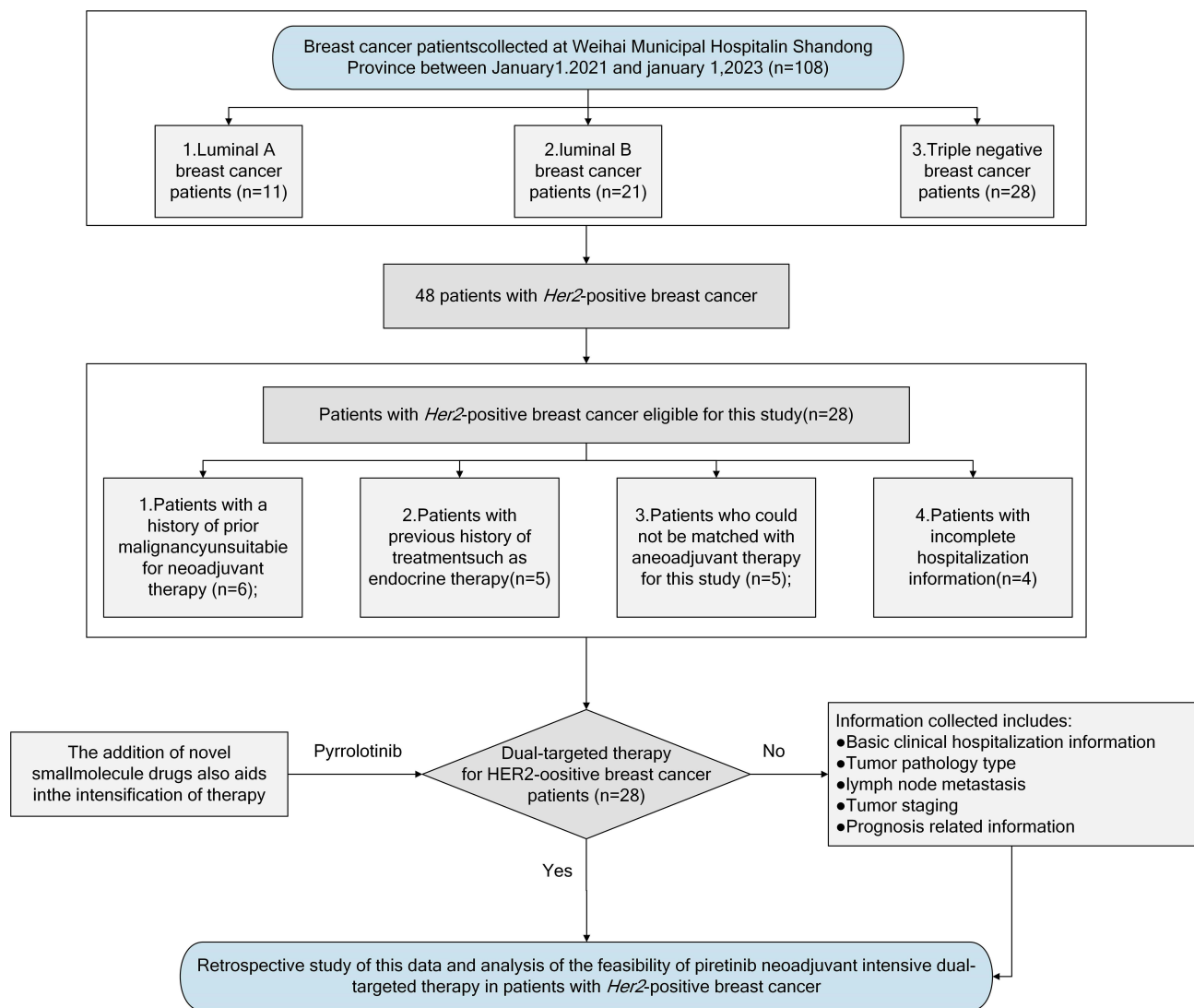


Figure 1 Schematic of the workflow of pyrrolitinib neoadjuvant dual-targeted therapy for patients with HER2-positive breast cancer included in this study.

Assessment Strategy

In this study, the Provincial Hospital of Weihai City, Shandong Province was selected as the study center, and patients with HER2-positive breast cancer determined by clinical diagnosis and histological testing were included. The dual-targeted treatment method was standardized uniformly in this study's treatment protocol, and the optimal regimen of pyrrolitinib was determined by adjusting the dose and course of treatment. To better assess the efficacy and safety of the treatment, all patients will receive standardized follow-up.

Clinical assessment will be performed in conjunction with the efficacy and adverse effects of pyrrolitinib. Patients will be assessed for disease control rate (DCR), partial remission rate (PR), complete remission rate (CR), and stable disease rate (SD) by RECIST 1.1 criteria, as well as monitored for adverse events and management.

Statistical Analysis Methods

Data were analyzed and processed by using SPSS statistical software version 21.0. According to different indicators, *t*-test, χ^2 test or Fisher's exact test were used to assess the differences between the treatment and control groups. Indicators such as mean, standard deviation, median and frequency were used to describe the demographic characteristics

of the samples, tumor characteristics and treatment protocols. A two-tailed test was used for statistical analysis, and a P value of less than 0.05 was considered statistically significant.

Results

Data Analysis of Patients' Baseline Clinical Baseline Profile Characteristics

A total of 28 patients with HER2-positive breast cancer who had dual-targeted therapy with the addition of the neoadjuvant therapy drug pyrrolitinib to their treatment were included in this study, and their collection workflow (Figure 1). Among these 28 patients with HER2-positive breast cancer, the mean age was 50.321 ± 11.100 years (31–75 years), with a total of 24 female patients with a mean age of 50.792 ± 11.708 years (31–75 years), and a total of 4 male patients with a mean age of 47.500 ± 5.545 years (43–57 years) (Table 1).

Comparison of Preoperative and Postoperative Conditions, Evaluation of Neoadjuvant Chemotherapy and Postoperative Miller-Payne Grading

By analyzing and comparing the preoperative and postoperative breast tumor sizes of these 28 patients, it was found that all HER2-positive breast cancer patients achieved significant reduction or even disappearance of their breast cancer lumps after adding the dual-targeted treatment of pyrotinib neoadjuvant drug, and the younger the age, the better the treatment effect. Data from a 44-year-old female patient showed that her mass completely disappeared after targeted therapy with this drug (Figure 2). The tumor diameter of these 28 patients achieved a reduction of 0.5–7.8 cm, in which the treatment effect was obvious in the age group of 31–45 years old patients, the younger the age of the patient, the more obvious the degree of tumor shrinkage, in which the youngest patient aged 31 years old achieved a reduction of 7.8 cm in the degree of the tumor (Figure 3).

Table 1 Characteristics of All HER2-Positive Breast Cancer Patients with Clinical Baseline Data

| Variable | Total (N=28) | Women (N=24) | Men (N=4) | Statistical Magnitude | P-value |
|----------|--------------------------|--------------------------|--------------------------|-----------------------|---------|
| Age | 50.321±11.100 | 50.792±11.708 | 47.500±5.545 | 0.532 | 0.599 |
| CEA | 2.160(1.410,2.630) | 2.280(1.410,2.640) | 1.910(1.600,1.910) | 1.018 | 0.325 |
| CA153 | 11.950(8.360,20.130) | 12.360(8.250,21.010) | 10.770(10.720,10.770) | 0.394 | 0.718 |
| AST | 21.200(14.400,23.500) | 20.900(13.900,23.500) | 22.100(21.200,22.100) | -0.624 | 0.554 |
| ALT | 15.500(13.500,24.000) | 16.900(13.500,24.000) | 15.300(14.200,15.300) | -0.131 | 0.922 |
| AST/ALT | 0.965±0.432 | 0.955±0.393 | 1.025±0.613 | -0.288 | 0.775 |
| AKP | 58.800(50.100,63.300) | 60.500(50.100,63.300) | 51.500(50.900,51.500) | 0.657 | 0.533 |
| GGT | 15.546±5.648 | 15.175±5.537 | 17.775±5.789 | -0.832 | 0.413 |
| TBIL | 12.700(10.600,14.800) | 12.800(11.300,14.800) | 12.700(8.800,12.700) | 0.263 | 0.818 |
| TP | 67.518±6.922 | 67.996±7.040 | 64.650±5.327 | 0.875 | 0.390 |
| Cr | 51.100±8.230 | 51.283±8.075 | 50.000±9.026 | 0.279 | 0.783 |
| UA | 268.924±91.855 | 271.420±96.653 | 253.950±52.436 | 0.340 | 0.737 |
| WBC | 6.970(5.510,9.310) | 7.470(5.510,9.310) | 6.770(5.570,6.770) | 0.394 | 0.718 |
| NEUT | 68.610±14.380 | 68.022±13.670 | 72.138±17.659 | -0.513 | 0.612 |
| TNC | 4.250(2.830,5.620) | 4.350(3.050,5.620) | 4.220(2.520,4.220) | 0.755 | 0.470 |
| Lym% | 30.046±13.929 | 30.619±13.086 | 26.610±17.801 | 0.516 | 0.610 |
| Lym | 1.878±0.735 | 1.885±0.691 | 1.835±0.956 | 0.121 | 0.904 |
| RBC | 4.313±0.460 | 4.349±0.463 | 4.098±0.379 | 0.994 | 0.329 |
| Hb | 133.000(121.000,143.000) | 133.000(121.000,143.000) | 135.000(128.000,135.000) | -0.033 | 1.000 |
| HCT | 38.975±3.379 | 38.854±3.298 | 39.700±3.746 | -0.448 | 0.658 |

Abbreviations: CEA, Carcinoembryonic Antigen; CA153, Carcinoma Antigen 153; AST, Alglutaminase; ALT, Alglutaminase; AST/ALT, Alglutaminase/Alglutaminase; AKP, Alkaline Phosphatase; GGT, Glutamyl Transferase; TBIL, Total Bilirubin; TP, Total Protein; Cr, Creatinine; UA, Serum Uric Acid; WBC, White Blood Cells; NEUT, Neutrophils; TNC, Troponin; Lym%, Percentage of Lymphocytes; Lym, Lymphocytes; RBC, Red Blood Cell Count; Hb, Hemoglobin; HCT, Hematocrit.

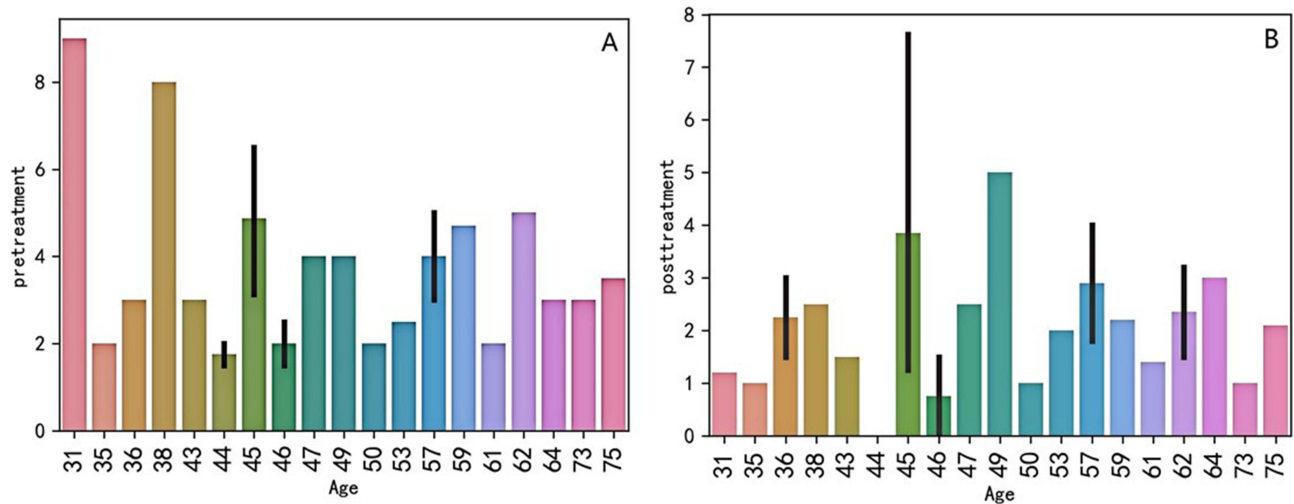


Figure 2 Distribution of tumor size before and after treatment in breast cancer patients of different ages. (A) shows a histogram of tumor size distribution before treatment and (B) shows a histogram of tumor size distribution after treatment).

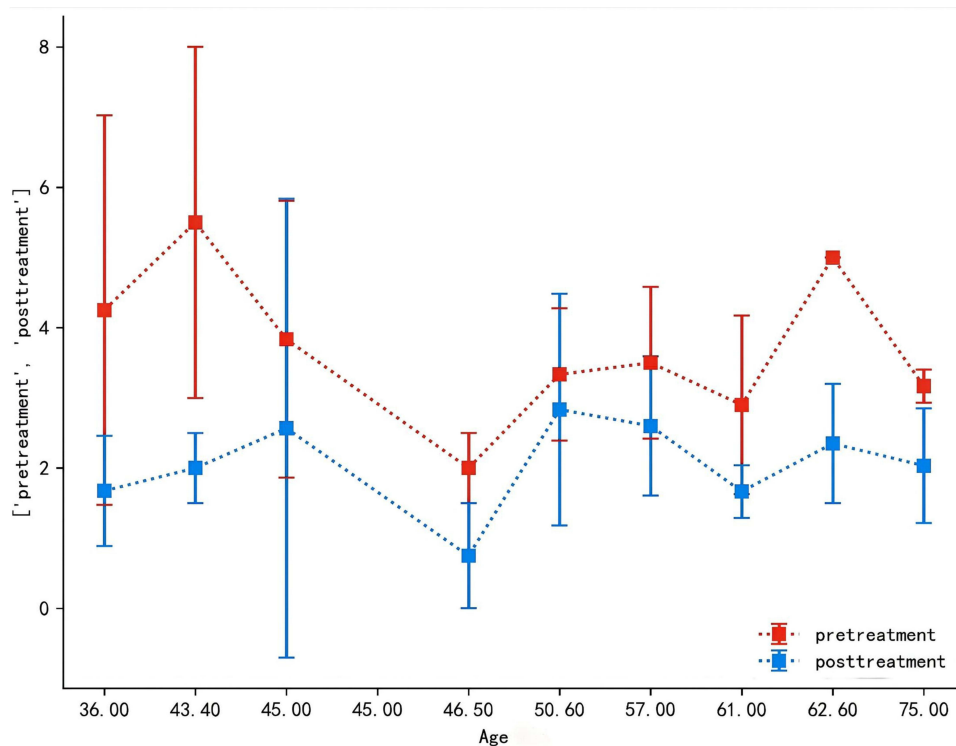


Figure 3 Comparative line graph of tumor size before and after treatment.

In this study, the majority of the HER2-positive patients were preoperatively assessed as highly suspicious for malignancy, with ultrasound evaluations of 4c and 5. Through preoperative and postoperative comparisons of pyrrolitinib-enhanced adjuvant therapy, we found that 50% of patients had postoperative Miller-Payne classification grade 4, with 7% of patients classified as grade 5 postoperatively, indicating a better prognosis for patients receiving pyrrolitinib-enhanced adjuvant therapy, and even the potential for complete postoperative cure (Table 2).

Table 2 Comparison of Preoperative and Postoperative Conditions of Pyrrolitinib-Enhanced Adjuvant Therapy

| Preoperative Situation | | Postoperative Situation | |
|-------------------------------------|-----------|---|-----------|
| Normative | Precedent | Normative | Precedent |
| Breast Tumor Location | 14 | Neoadjuvant chemotherapy evaluation results | |
| Left | 13 | Efficacy evaluated as SD | 8 |
| Right | 1 | Efficacy evaluated as PR | 8 |
| Two-sided | | Uncharted territory | 12 |
| Pre-operative ultrasound evaluation | | Postoperative Miller-Payne classification | |
| Category 4a | 1 | Level 1 | 4 |
| Category 4b | 5 | Level 2 | 1 |
| Category 4c | 10 | Level 3 | 1 |
| Category 5 | 12 | Level 4 | 14 |
| | | Level 5 | 2 |
| | | STEPP recurrence risk score | |
| | | <1.42 | 0 |
| | | >1.42 | 6 |

Discussion

With the rapid advancements in gene technology and molecular biology, an increasing number of biomarkers have been discovered and utilized in the individualized treatment of tumors. Among these biomarkers, HER2 has emerged as a pivotal indicator in immunohistochemistry, significantly guiding the personalized treatment of HER2-positive breast cancer.^{12,13} HER2-positive breast cancer accounts for approximately 20% of all breast cancers and is characterized by high malignancy and recurrence rates.¹⁴ While HER2-targeted therapies have been instrumental in improving the prognosis for HER2-positive patients, their application remains limited, particularly when single-agent treatments yield suboptimal results.^{5,15} Furthermore, issues of drug resistance and adverse side effects present substantial challenges to the broader use of HER2-targeted therapies.¹⁶

In recent years, the emergence of dual-targeted therapies, particularly the combination of trastuzumab and pertuzumab, has represented a significant shift in the treatment landscape for HER2-positive breast cancer.^{13,17} For instance, Piratinib, an oral dual HER2 inhibitor that targets both HER2 and the epidermal growth factor receptor (EGFR), has shown promising potential in the management of HER2-positive breast cancer.^{18,19} The primary objective of this study was to evaluate the feasibility of pyrrolitinib-based dual-targeted therapy in the neoadjuvant setting for patients with HER2-positive breast cancer. The fundamental premise of this study is based on the combination of targeted therapy and neoadjuvant therapy in HER2-positive breast cancer. HER2 is a protein that is overexpressed in various breast cancer cells, and its overexpression is closely associated with the malignancy and prognosis of tumors. While traditional HER2-targeted drugs such as trastuzumab have been widely used, their efficacy as monotherapy is limited and can lead to drug resistance. Therefore, this study focuses on a new generation of orally administered dual-targeted HER2 inhibitor, pyrrolitinib, with the aim of enhancing treatment effectiveness by simultaneously targeting HER2 and EGFR, overcoming drug resistance, and providing more effective treatment options for patients.

In this study, we conducted a retrospective analysis of data from 28 patients diagnosed with HER2-positive breast cancer who received dual HER2-targeted therapy at the Provincial Hospital of Weihai City, Shandong Province, China, from January 1, 2019, to December 31, 2022. All patients underwent neoadjuvant therapy with pyrrolitinib, and tumor response and risk were systematically assessed. The results demonstrated that pyrrolitinib significantly reduced tumor mass in patients receiving neoadjuvant dual-targeted therapy. Most patients were rated as 3 or 4 on the risk assessment scale, indicating a 30% to 90% reduction in tumor cell counts post-treatment. These findings suggest that pyrrolitinib may represent an effective therapeutic strategy in the intensification of dual-targeted treatment for HER2-positive breast cancer.

Several studies have previously evaluated the efficacy of dual HER2-targeted therapies.²⁰ For example, the Swain SM et al²¹ demonstrated that the combination of pyrrolitinib and trastuzumab resulted in higher rates of pathologic complete remission in the neoadjuvant setting compared to single-agent HER2 therapies. Similarly, the Piccart M et al²² indicated that the combination of pivozotinib and trastuzumab as adjuvant therapy improved prognostic outcomes for patients with HER2-positive breast

cancer. Our findings align with these studies, further reinforcing the efficacy of dual HER2-targeted therapies as a robust treatment strategy for this patient population.

The novelty of our study lies in the selection of pyrrolitinib as a dual HER2-targeted agent, which offers the convenience of oral administration compared to injectable therapies, thereby reducing treatment invasiveness and associated adverse effects while also alleviating the economic burden on patients. By employing dual HER2-targeted therapy as neoadjuvant treatment, we conducted a thorough assessment of tumor response and risk ratings, enhancing our understanding of the efficacy of neoadjuvant therapy and its implications for postoperative prognosis. This study distinguishes itself by quantitatively assessing treatment efficacy through a rigorous postoperative tumor response and risk rating system, confirming the significant impact of dual HER2-targeted therapy.

However, our study does have several limitations. First, the retrospective design introduces potential selection and information biases. Second, the relatively small sample size necessitates larger prospective studies to validate our findings. This constraint is primarily attributable to the emerging nature of the drugs used in our neoadjuvant treatment approach, which have not yet been widely implemented in clinical practice. Additionally, the treatment regimen focused on the combination of pyrrolitinib and trastuzumab, leaving the efficacy of other drug combinations unexplored. Finally, our study was limited to patients with HER2-positive breast cancer, indicating a need for further research to evaluate the treatment's effectiveness across other breast cancer subtypes.

In summary, this study provides new evidence regarding the role of pyrrolitinib as a dual HER2-targeted therapeutic agent, confirming the significance of this regimen in the neoadjuvant treatment of breast cancer. The implications of our findings are noteworthy for future breast cancer research, as they offer guidance for conducting additional clinical trials focused on neoadjuvant therapy and serve as a catalyst for enhancing early detection and effective treatment strategies for breast cancer. We anticipate that further investigation will elucidate the mechanisms of action for pyrrolitinib and explore its potential applications in various oncological contexts.

Conclusion

This study provides compelling evidence for the feasibility of pyrrolitinib as a novel anti-HER2 targeted therapy in the neoadjuvant treatment of HER2-positive breast cancer patients. Our findings not only reinforce the biological viability of pyrrolitinib as an oral therapeutic agent but also highlight its effectiveness in a dual-targeted approach, marking a significant advancement in the management of this aggressive cancer subtype. The results indicate that pyrrolitinib can substantially reduce tumor size and enhance the overall treatment response, offering a promising strategy for individualized patient care. This approach has the potential to pave the way for more personalized treatment regimens, catering to the unique needs of each patient while minimizing the adverse effects commonly associated with traditional therapies.

Furthermore, our research underscores the necessity for ongoing exploration into innovative treatment options that are both efficacious and less toxic. The insights gained from this study not only contribute to the growing body of knowledge surrounding HER2-positive breast cancer but also serve as a foundation for future investigations aimed at optimizing therapeutic strategies. As the field moves towards more targeted and personalized treatments, pyrrolitinib stands out as a valuable addition to the armamentarium against breast cancer, advocating for improved patient outcomes and a better quality of life.

Data Sharing Statement

The data and all materials are the property of the authors, and data supporting the study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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