Original Article

Trastuzumab plus pertuzumab in combination with chemotherapy in metastatic HER2-positive breast cancer: a retrospective single-armed cohort study in China

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Background: There are currently few studies on the efficacy and safety of the dual human epidermal growth factor receptor 2 (HER2)-targeted combination of trastuzumab and pertuzumab in second-line or subsequent therapy of metastatic breast cancer (MBC). This study retrospectively demonstrated the clinical efficacy and side effects of trastuzumab plus pertuzumab in combination with chemotherapy in HER2-positive MBC.

Methods: Patients with HER2-positive MBC and treated with trastuzumab plus pertuzumab combined with chemotherapy at our hospital between August 2013 and October 2021 were included. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were disease control rate (DCR), objective response rate (ORR), clinical benefit rate (CBR), and side effects. PFS was calculated using the Kaplan-Meier method and side effects were assessed according to Common Terminology Criteria for Adverse Events 5.0.

Results: A total of 55 women were included and the median PFS for trastuzumab plus pertuzumab combined with chemotherapy was 10 months. For the different treatment lines, the median PFS was 19, 8, and 5 months in first, second, and third and beyond, respectively. The DCR, ORR, and CBR were 81.8%, 47.3%, and 56.4%, respectively. The median PFS of patients with primary trastuzumab resistance was significantly shorter than trastuzumab-sensitive patients (5 *vs.* 12 months, P=0.011). The most common adverse reactions were neutropenia (40.0%), leukopenia (34.5%), thrombocytopenia (32.7%), and diarrhea (29.1%). The most common grade 3–4 adverse reactions were leukopenia (12.7%), thrombocytopenia (9.1%), and diarrhea (9.1%).

Conclusions: For patients with HER2-positive MBC, treatment with trastuzumab plus pertuzumab combined with chemotherapy appeared efficacious and safe.

Keywords: Trastuzumab; pertuzumab; human epidermal growth factor receptor 2 positive (HER2-positive); metastatic breast cancer (MBC); side effects

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Introduction

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer accounts for about 20% of all types of breast cancer (1-3). Trastuzumab is the cornerstone of treatment for patients with HER2-positive breast cancer, reducing the risk of recurrence and improving the prognosis of these patients (4). In order to further improve the efficacy of HER2-positive metastatic breast cancer (MBC) treatment, the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study confirmed that compared with trastuzumab alone, trastuzumab plus pertuzumab and chemotherapy prolonged patients' median progression-free survival (PFS) and overall survival (OS) (5,6). This established the standard treatment status of dual HER2 blockade in first-line treatment of HER2-positive MBC. However, there are currently few studies on the efficacy and safety of the dual HER2-targeted combination of trastuzumab and pertuzumab in second-line or subsequent therapy. Therefore, we retrospectively analyzed the efficacy and safety of trastuzumab plus pertuzumab and chemotherapy in patients with HER2-positive MBC. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3592/rc).

Methods

General information

Patients with metastatic HER2-positive breast cancer treated with trastuzumab plus pertuzumab and chemotherapy at Jiangsu Cancer Hospital between August 2013 and October 2021 were included. All patients were pathologically confirmed to have HER2-positive MBC. HER2 status was determined using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). IHC 3+ or IHC 2+ plus FISH positive was deemed to be HER2-positive. We mainly used medical records as data source. Follow-up was conducted through outpatient tracking and telephone. The last follow-up time was October 31, 2021, and the median follow-up time was 12 months. Two patients were lost to follow-up during maintenance therapy. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Jiangsu Cancer Hospital (No. 2022-004), and individual consent for this retrospective analysis was waived.

Treatment method

All patients received trastuzumab plus pertuzumab and chemotherapy until disease progression or intolerable adverse reactions. Trastuzumab was given with a loading dose of 8 mg per kilogram of body weight, followed by 6 mg per kilogram every 3 weeks. Pertuzumab was given at 840 mg as a loading dose, followed by 420 mg every 3 weeks. Taxane was used in taxane-sensitive patients while vinorelbine and other chemotherapy drugs were used in taxane-resistant patients. Nab-paclitaxel was given at 125 mg/m^2 on days 1 and 8, docetaxel was given at 75 mg/m^2 every 3 weeks, and other chemotherapy drugs were implemented at standard doses. As to maintenance treatment, hormone receptor (HR)-negative patients received anti-HER2-targeted therapy alone, and HR-positive patients received anti-HER2-targeted therapy and endocrine therapy.

Efficacy and adverse reaction evaluation

All patients received trastuzumab plus pertuzumab and chemotherapy for at least 2 cycles, 21 days per cycle, and an efficacy evaluation was performed every 2 cycles. During maintenance therapy, the assessment was made every 3–4 cycles. All patients underwent imaging tests including computed tomography (CT) and magnetic resonance imaging (MRI) at baseline and during treatment. Treatment response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). All patients underwent cardiac ultrasound examinations at baseline and every 3 months during the treatment. Blood tests, including routine blood tests, and liver and kidney function tests, were also conducted before each cycle of the treatment. Adverse events were obtained through clinical follow-up and laboratory examination results and were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0).

Study endpoint

The primary endpoint of the study was PFS, defined as the time from the first day of treatment to disease progression or death from any cause. Secondary endpoints were objective response rate (ORR), disease control rate (DCR), and clinical benefit rate (CBR). ORR was defined as the proportion of patients who had a partial response (PR) or

complete response (CR) to therapy. DCR was defined as the proportion of patients who achieved CR, PR, and stable disease (SD) in response to therapy. CBR was defined as the percentage of advanced cancer patients who achieved CR, PR, or at least 6 months of SD in response to therapy.

Statistical analysis

Descriptive statistics were used to summarize disease-related characteristics of patients and drug-related adverse reactions during therapy. Survival analysis was calculated by the Kaplan-Meier method, and univariate analysis was performed by log-rank test. All statistical evaluations were performed using SPSS version 26.0 (IBM, Armonk, NY, USA). P<0.05 indicated a statistically significant difference.

Results

Baseline characteristics

We analyzed the information of 55 patients with HER2-positive MBC who presented to our hospital. All patients were female (median age, 52 years) and had received the dual HER2-targeted therapy of trastuzumab and pertuzumab in combination with chemotherapy. Among them, 23 patients (41.8%) received first-line treatment, 11 (20.0%) received second-line treatment, and 21 (38.2%) received third-line or beyond treatment. The median number of treatment lines was 2 (range, 1–10; *Table 1*). A total of 25 (45.5%) patients had used trastuzumab after relapse and belonged to the secondary trastuzumab-resistant patients, and 28 (50.9%) patients were primary trastuzumab-resistant patients. Primary resistance to trastuzumab was defined as disease progression in MBC within 3 months from the last dose of trastuzumab, or recurrence in early-stage breast cancer during (neo)adjuvant trastuzumab therapy or within 12 months from the last dose of trastuzumab. Six patients (10.9%) with HER2-negative primary tumors had HER2-positive metastatic tumors, and these patients were treated with HER2-targeted therapy after recurrence.

Efficacy

The median PFS for all patients was 10 months (95% CI: 6.22–13.78 months; *Figure 1*). A total of 26 patients reached the endpoint of the study, 2 patients were lost to follow-up during maintenance therapy, and the remaining 27 patients are still under treatment. Median PFS in first-line, second-line, and third-line and beyond treatment was 19, 8, and 5 months, respectively (*Figure 2*). All patients were evaluated for efficacy, with 1 case with CR, 25 cases with PR, 19 cases with SD, and 10 cases with progressive disease (PD). The DCR was 81.8%, the ORR was 47.3%, and the CBR was 56.4%. Patients with HER2-negative primary tumors and HER2-positive metastatic tumors had no significant difference in efficacy compared with patients with HER2-positive primary tumors. The PFS was 8 and 10 months, respectively (P=0.846). The efficacy of dual HER2-targeted therapy in first-line treatment was better than that of second-line and beyond treatment (19 *vs.* 6 months, P=0.001). In patients who had not received HER2-targeted therapy after relapse, the efficacy of dual HER2-targeted therapy in combination with chemotherapy was better (19 *vs.* 5 months, P<0.001). Among multiline treated patients, the median PFS of trastuzumab or small molecule tyrosine kinase inhibitor (TKI)-pretreated patients was 6 and 5 months, respectively, which was shorter than untreated patients. Patients with primary resistance to trastuzumab had a poorer prognosis compared with patients with nonprimary resistance to trastuzumab (5 *vs.* 12 months, P=0.011; *Figure 3*). In addition, among the 38 patients with nonprimary resistance to trastuzumab, the median PFS of 9 patients in third-line or beyond treatment was 13 months (95% CI: 3.77–22.22 months), and the median PFS of 12 patients who had been pretreated with TKI was 5 months (95% CI: 0.26–9.74 months). In the selection of chemotherapy drugs, the combination of taxanes had the best effect (11 *vs.* 2 months, P=0.002; *Table 2*).

Safety and adverse events

The most common adverse events were anemia (40.0%), neutropenia (34.5%), leukopenia (32.7%), and diarrhea (29.1%). Diarrhea usually occurred in the first 2 cycles of treatment and improved after treatment with loperamide hydrochloride. As shown in *Table 3*, the most common grade III–IV adverse events were neutropenia (12.7%), leukopenia (9.1%), and thrombocytopenia (9.1%). No patients developed agranulocytosis with fever. Hematological toxicity mainly occurred during chemotherapy and was considered to be related to chemotherapy drugs. Overall, the combination of trastuzumab and pertuzumab has a good safety profile, and none of the patients developed drug-related cardiac insufficiency.

Table 1 Baseline characteristics of 55 patients

Characteristics	First-line (n=23)	Second-line (n=11)	Third-line and beyond (n=21)	All patients (n=55)
Age, median [range]		52 [29–73]		
>60 years	4	2	5	11
≤60 years	19	9	16	44
HER2 status in primary tumor				
Positive	22	9	18	49
Negative	1	2	3	6
HR status				
Positive	19	5	14	32
Negative	4	6	7	23
Visceral metastases				
No	5	3	4	12
Yes	18	8	17	43
Lung metastases	11	4	9	24
Liver metastases	10	5	12	27
Brain metastases	2	2	6	10
HER2-targeted therapy after recurrence				
Trastuzumab	0	6	19	25
TKI	0	5	19	24
T-DM1	0	0	8	8
Combined with chemotherapy				
Taxane	22	9	13	44
Vinorelbine	1	1	6	8
Platinum	4	1	0	5
Gemcitabine	0	0	2	2
Primary trastuzumab resistant				
No	23	4	0	27
Yes	0	7	21	28

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TKI, tyrosine kinase inhibitor; T-DM1, trastuzumab emtansine.

Discussion

Trastuzumab acts synergistically when combined with pertuzumab (7-9). The CLEOPATRA study showed that dual HER2-targeted therapy plus chemotherapy improved the median PFS of MBC patients from 12.4 to 18.7 months, and the median OS reached 57.1 months (5,6). The PUFFIN study confirmed the same benefit in the Chinese population (10), and the dual HER2-targeted therapy is now the standard treatment regime for HER2-positive MBC patients. In our study, median PFS in the first-line setting was 19 months, which was longer than the PUFFIN trial (14.5 months). In both the CLEOPATRA and PUFFIN clinical trials, endocrine therapy was generally not routinely used in combination with targeted therapy in patients with HR-positive and HER2-positive MBC. However, in our study, HR-positive patients received combined maintenance

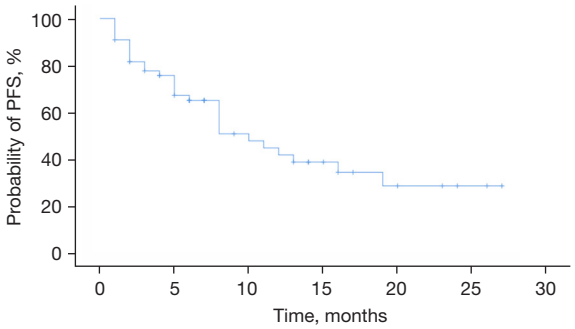

Figure 1 PFS curves of 55 patients with metastatic HER2-positive breast cancer treated with trastuzumab plus pertuzumab in combination with chemotherapy. PFS, progression-free survival; HER2, human epidermal growth factor receptor 2.

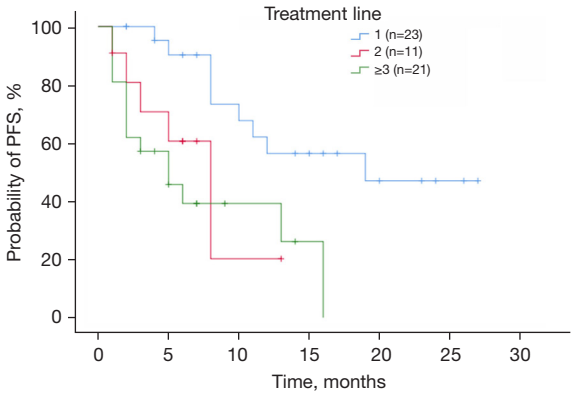

Figure 2 PFS curves of patients treated with trastuzumab plus pertuzumab in combination with chemotherapy in different treatment lines. PFS, progression-free survival.

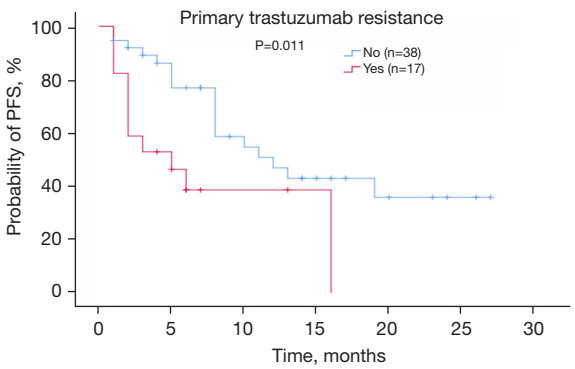

Figure 3 PFS curves of trastuzumab plus pertuzumab in combination with chemotherapy in patients with and without primary resistance to trastuzumab. PFS, progression-free survival.

of endocrine therapy and targeted therapy after 6–8 cycles of chemotherapy. We found that the addition of endocrine therapy did not increase the incidence of adverse events and could improve the antitumor effect to a certain extent. In clinical practice, patients have good compliance with endocrine therapy, and this maintenance therapy is highly operable.

The chemotherapy drug used in the CLEOPATRA and PUFFIN studies was docetaxel. In our study, 44 (80.0%) patients used taxanes (including nab-paclitaxel, paclitaxel liposome, or docetaxel), and of these, 4 patients (7.3%) were treated with taxanes in combination with platinum drugs. The median PFS of the taxane group was 11 months. The median PFS of the remaining 11 taxane-resistant patients was only 2 months. Among them, 8 (14.5%) patients were treated with vinorelbine, and the median PFS was 5 months. It seems taxanes are the preferred chemotherapeutic drugs for dual HER2-targeted therapy. However, given the small sample size and the uneven distribution of the drug in our study, the results may have been biased. Therefore, further research is needed.

Although dual HER2-targeted therapy has achieved good efficacy in first-line treatment of HER2-positive MBC, there are few studies involving later-line treatment. Real-world data on Chinese populations are scarce. A preliminary study has shown the complementary mechanism of pertuzumab and trastuzumab. Pertuzumab still shows a certain antitumor activity, even in a trastuzumab-resistant HER2-positive mouse model (11). Pertuzumab was launched in China in 2019. Some patients did not have the chance to use pertuzumab in the first-line treatment, and there was a lack of data on the dual HER2-targeted therapy in later-line treatment. Considering the poor availability of trastuzumab deruxtecan (DS-8201) in China, there is currently no standard treatment strategy for third-line and above treatment of HER2-positive MBC. In clinical practice, trastuzumab combined with other chemotherapy drugs is usually used in these patients. However, in second-line and later-line treatment, the effect of trastuzumab-based therapy is not satisfactory. In a study by Cancello *et al.*, the median PFS was 5.25, 5.25, and 3.75 months in second-line, third-line, and fourth-line treatment, respectively (12). In pretreated HER2-positive advanced breast cancer patients in the TH3RESA study, the median PFS of trastuzumab emtansine (T-DM1) was 6.2 months, and the median PFS of physician's choice

Table 2 Efficacy of dual HER2-targeted therapy in combination with chemotherapy in 55 metastatic breast cancer patients

Characteristics	Patients (n=55)	Median PFS (months)	95% CI	P value
HR status				0.118
Positive	32	8	4.10–11.91	
Negative	23	12	3.11–20.88	
HER2 status in primary tumor				0.846
Positive	49	10	5.82–14.18	
Negative	6	8	2.12–13.88	
Treatment line				0.003
First-line	23	19	–	0.001
Second-line	11	8	5.49–10.51	
Third-line and beyond	21	5	1.31–8.69	
Visceral metastases				
No	12	–	–	–
Yes	43	8	3.94–12.05	0.457
Lung metastases	24	12	6.95–17.05	0.546
Liver metastases	27	8	3.46–12.54	0.542
Brain metastases	10	5	3.66–6.35	0.135
HER2-targeted therapy after recurrence	30	5	1.42–8.58	<0.001
Trastuzumab	25	6	1.66–10.35	0.004
TKI	24	5	2.00–8.00	0.001
T-DM1	2	1	–	0.981
Combined with chemotherapy				
Taxane	44	11	4.71–17.30	0.002
Non-taxane	11	2	0.00–5.05	0.002
Vinorelbine	8	5	0.00–15.30	0.090
Primary trastuzumab resistant				0.011
No	38	12	6.10–17.90	
Yes	17	5	0.24–9.76	

CI, confidence interval; PFS, progression-free survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TKI, tyrosine kinase inhibitor; T-DM1, trastuzumab emtansine.

(including trastuzumab and/or lapatinib combined with chemotherapy) was only 3.3 months (13). In the TH3RESA study, pertuzumab in combination with trastuzumab was not included in the physician's choice. In our study, the median PFS of dual HER2-targeted therapy was 8 months in second-line patients, and the median PFS in second-line and above patients was 6 months, which was similar to the efficacy in people treated with T-DM1. However, from an economic point of view, domestic patients have better accessibility to trastuzumab and pertuzumab.

In our study, the median PFS of patients without primary resistance to trastuzumab was significantly better than those with primary resistance to trastuzumab (12 *vs.* 5 months, P=0.011). Yang *et al.* reported that in third-line treatment, the median PFS of trastuzumab-treated patients with primary and secondary resistance to trastuzumab was

Table 3 Adverse reactions that occurred in 55 patients with advanced breast cancer during treatment with dual HER2-targeted therapy

Adverse events	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	All grades, n (%)
Anemia	11 (20.0)	9 (16.4)	2 (3.6)	0 (0.0)	22 (40.0)
Neutrophil count decreased	10 (18.2)	2 (3.6)	6 (10.9)	1 (1.8)	19 (34.5)
White blood cell decreased	5 (9.1)	8 (14.5)	4 (7.3)	1 (1.8)	18 (32.7)
Diarrhea	9 (16.4)	6 (10.9)	1 (1.8)	0 (0.0)	16 (29.1)
Platelet count decreased	4 (7.3)	2 (3.6)	4 (7.3)	1 (1.8)	11 (20.0)
Aspartate aminotransferase increased	7 (12.7)	2 (3.6)	0 (0.0)	0 (0.0)	9 (16.4)
Alanine aminotransferase increased	4 (7.3)	1 (1.8)	0 (0.0)	0 (0.0)	5 (9.1)
Fatigue	3 (5.5)	1 (1.8)	0 (0.0)	0 (0.0)	4 (7.3)
Anorexia	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)

HER2, human epidermal growth factor receptor 2.

4.1 and 6.1 months, respectively (14). In our study, when using dual HER2-targeted therapy as third-line or beyond treatment, the median PFS of patients with primary and secondary resistance to trastuzumab was 2 and 13 months, respectively. In patients without primary resistance to trastuzumab, even if they had received prior TKI therapy, the median PFS still reached 8 months. Bian *et al.* reported that the median PFS of lapatinib and trastuzumab-pretreated patients was only about 3.4 months when they were treated with trastuzumab again (15). For patients with primary resistance to trastuzumab, the addition of pertuzumab may not improve the efficacy. This may be due to the fact that although pertuzumab and trastuzumab act on different HER2 targets, their mechanisms of action are similar (8,16). For patients without primary trastuzumab resistance, trastuzumab in combination with pertuzumab showed synergistic antitumor efficacy and remained a viable option even after multiple lines of treatment.

At present, it is still unclear whether the discordance of HER2 expression between primary breast cancer and MBC is related to prognosis (17,18). In our study, there were 6 patients with HER2-negative primary breast cancer and HER2-positive recurrent breast cancer. No significant difference was found between the PFS of these patients and those with primary HER2-positive breast cancer. This may be related to factors such as the small sample size of the discordance of HER2 expression between primary breast cancer and MBC, the lack of re-evaluation of HER2 status in metastatic lesions, and the unbalanced number of previous treatment lines of patients. The relationship between the discordance of HER2 expression and prognosis remains to be explored by further expanding the sample size.

In terms of safety, the most common adverse reactions in previous clinical studies of dual HER2-targeted therapy combined with chemotherapy were hematological toxicity, abnormal liver function, and diarrhea. Hematological toxicity and abnormal liver function were thought to be related to chemotherapy (6,10), and diarrhea was considered to be associated with both HER2-targeted therapy and chemotherapy. This is consistent with our findings. The higher incidence of anemia in our study may be related to the high proportion of patients with multiple lines of therapy. No patient developed any clinical symptoms related to cardiotoxicity during treatment. During treatment, only a small percentage of patients had a mild decrease (<10%) in left ventricular ejection fraction (LVEF), and LVEF was greater than 50% in all patients.

In conclusion, trastuzumab plus pertuzumab in combination with chemotherapy showed good efficacy and safety in patients with HER2-positive MBC. For patients without primary resistance to trastuzumab, significant clinical effects were achieved, even after TKI treatment and in third-line or beyond treatment. However, this study is a single-center retrospective study with a small sample size and a lack of monitoring of adverse reactions in some patients. The sample size and the follow-up time need to be further expanded.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3592/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3592/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3592/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 ethics board of Jiangsu Cancer Hospital (No. 2022-004), and individual consent for this retrospective analysis was waived.

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