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Original Article

Comparison of pyrotinib or lapatinib with chemotherapy for patients with HER2 positive breast cancer after first-line treatment failure: a retrospective study

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Abstract: Objective: To explore the difference in efficacy and safety of pyrotinib or lapatinib combined with chemotherapy in human epidermal growth factor receptor-2 (HER-2) positive breast cancer patients who failed the first-line trastuzumab-containing treatment. Methods: The present retrospective study included 164 HER-2 positive breast cancer patients admitted to our hospital. Among them, 68 cases received pyrotinib combined with chemotherapy after the failure of trastuzumab first-line treatment (pyrotinib group), and the other 96 cases received lapatinib combined chemotherapy (lapatinib group). The end of the follow-up time was set as June 1, 2020. The primary endpoint was progression free survival (PFS), and the secondary endpoints included best objective response rate (ORR) and safety. Results: Till the end of the follow-up, the best ORR (60.3% vs. 34.4%) in the pyrotinib group was significantly higher than that in the lapatinib group, and the median PFS (9.0 months vs. 6.2 months) was also largely prolonged (P<0.01). In addition, the median PFS of the patients with brain metastases in the pyrotinib group was 6.5 months, and was much longer that in the lapatinib group which wereth 3.5 months in length (P<0.05). Multivariate COX regression analysis showed that pyrotinib combined with chemotherapy (HR=0.653, P<0.05) was associated with longer PFS of patients, while the lapatinib group had a higher proportion of vomiting and hand foot syndrome than the pyrotinib group (P<0.05). Conclusion: After the failure of first-line trastuzumab-containing treatment, combination of pyrotinib with chemotherapy has more significant short-term efficacy in HER-2 positive breast cancer patients than lapatinib combined with chemotherapy, especially in patients with brain metastasis.

Keywords: Pyrotinib, human epidermal growth factor receptor-2, breast cancer, trastuzumab, safety

Introduction

Breast cancer (BC) is one of the most common malignant diseases related to global female deaths currently, and the incidence trends increased in younger women in recent years [1, 2]. Human epidermal growth factor receptor-2 (HER-2) positive breast cancer is one of the common pathological types of breast cancer with high malignancy, rapid disease progression, and poor prognosis [3]. Anti HER-2 therapy is the most important treatment for HER-2 positive breast cancer patients now. The development and application of anti HER-2 targeted drugs such as trastuzumab and lapatinib have greatly prolonged the survival of BC patients. At present, trastuzumab is the first-line treatment for patients with HER-2 positive advanced breast cancer [4, 5]. However, the treatment of HER-2 positive advanced breast cancer patients after the failure of trastuzumab treatment is still a great clinical challenge. The National Comprehensive Cancer Network (NCCN) expert's group's study suggested that the patients could adopt the therapeutic schedule containing lapatinib after the failure of trastuzumab treatment. Some studies have proved that lapatinib regimen is effective for patients with HER-2 positive advanced breast cancer after trastuzumab treatment failure, but the progression free survival (PFS; about 6.5 months) of most patients after treatment is far from satisfactory [1, 6, 7]. Thus, a more effective treatment scheme is still urgently needed.

Pyrotinib is a small molecule, irreversible tyrosine kinase inhibitor independently developed

in China, and clinical studies about pyrotinib in the phase II and phase III clinical trials have achieved encouraging results [8-10]. For example, the multi-center randomized controlled study of Ma et al. demonstrated that pyrotinib combined with capecitabine had a high objective response rate (ORR) of 78.5% and the median PFS of 18.1 months in the treatment of HER2 positive advanced breast cancer [11]. Pyrotinib was launched in China in August 2018 and has been approved for the treatment of HER-2 positive advanced breast cancer. However, the treatment data of pyrotinib in clinic is still limited currently. Besides, it is unclear that the difference in curative effects between pyrotinib and other anti-HER-2 therapies in the treatment of HER-2 positive breast cancer patients after trastuzumab failure. Therefore, we retrospectively analyzed the treatment data of 164 patients with HER-2 positive breast cancer after the failure of trastuzumab first-line treatment, and compared the efficacy difference between pyrotinib and lapatinib, aiming to provide reference for further clinical practice.

Materials and methods

Patient data

A total of 164 patients with HER-2 positive breast cancer who experienced unsuccessful first-line trastuzumab treatment in our hospital between December 2018 and March 2020 were included in the study. This study was approved by the Ethics Committee of our hospital and all patients signed the informed consent.

Inclusion criteria: (1) The patient was diagnosed with breast cancer by histology or cytology detection. (2) The results of immunohistochemistry for HER-2 was 3+ or the result of fluorescence in situ hybridization (FISH) was + in the tumor tissues (primary or metastatic lesions) of the selected patients. (3) Patients who had metastasis or relapse after first-line treatment with trastuzumab were treated with pyrotinib or lapatinib combined with chemotherapy. (4) Patients aged ≥18 years. (5) patients had the score of Eastern Cooperative Oncology Group (ECOG) ≤2. (6) patients had adequate blood, kidney and liver functions.

Exclusion criteria: (1) Women were diagnosed as HER-2 negative breast cancer. (2) Patients received 2-line or more multi-line treatment after the recurrence or metastasis of breast cancer. (3) Patients had the expected survival time of less than 3 months. (4) Patients had contraindications of pyrotinib and lapatinib. (5) Patients had incomplete clinical and follow-up data.

After the failure of first-line treatment by trastuzumab, 68 patients received pyrotinib combined with chemotherapy, and were set as the pyrotinib group. The rest 96 patients received lapatinib combined with chemotherapy were set as the lapatinib group. The general clinical data of the two groups are shown in **Table 1**.

Treatment methods

The patients in the pyrotinib group received 320mg of oral pyrotinib maleate tablets (China Jiangsu Hengrui Pharmaceutical Co., Ltd., National drug approval number: H20180013, specification: 160 mg), once a day. Pyrotinib was continuously used until the disease was progressed or the patients could not tolerate it. At the same time, the patients were treated with chemotherapy and the chemotherapy drugs used here are shown in **Table 1**. The curative effect was evaluated every 2 cycles (6 weeks).

The patients in the lapatinib group received 250 mg of oral lapatinib toluenesulfonate tablets (GlaxoSmithKline (Tianjin) Co., Ltd., specification: 250 mg), once a day. Lapatinib was continuously used until the disease was progressed or patients could not tolerate. The patients were also treated with chemotherapy and the dosage, administration mode and frequency of the chemotherapy drug were all the same as those of pyrotinib group. The chemotherapy drugs used here are shown in **Table 1** and the curative effect was evaluated every 2 cycles (6 weeks).

Evaluation criterion

Efficacy evaluation: Clinical efficacy of the patients was evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1) and was divided into the following grades: complete remission (CR): the tumor disappeared completely according to the imaging examination; partial remission (PR): The diameter of the tumor was reduced more than 30%; stable disease (SD): The tumor shrank, but the

Table 1. Comparison of baseline data between the two groups ($\bar{x}$ ± sd)

Items	Pyrotinib group (n=68)	Lapatinib group (n=96)	χ^2/t	P
Age (years)	43.9±11.4	46.3±9.9	1.402	0.163
ECOG score (scores)	1.5±0.4	1.6±0.3	1.743	0.084
HR status			0.057	0.477
Positive	35 (51.5)	44 (45.8)		
Negative	33 (48.5)	52 (54.2)		
Number of transfer sites			2.773	0.435
1	20 (29.4)	36 (37.5)		
2	30 (44.1)	38 (39.6)		
3	14 (20.6)	13 (13.5)		
≥4	4 (5.9)	9 (9.4)		
Transfer site (n, %)				
Central nervous system	13 (19.1)	25 (26.0)	1.072	0.300
Viscera	51 (75.0)	69 (71.9)	0.198	0.656
Non-visceral metastasis	17 (25.0)	27 (28.1)	0.198	0.656
Combined chemotherapy regimen				
Capecitabine	54 (79.4)	68 (70.8)	1.538	0.215
Navelbine	20 (26.4)	7 (7.3)	14.162	0.000
Gemcitabine	11 (16.2)	2 (2.1)	10.832	0.000
Taxanes	22 (32.4)	12 (12.5)	9.547	0.002
Others	3 (4.4)	1 (1.0)	1.900	0.168

Note: ECOG: Eastern Cooperative Oncology Group; HR: hormone.

shrinkage was less than 30%; progressive disease (PD): The diameter of tumor increased by more than 20%, or new lesions appeared [12].

Evaluation of adverse reactions: The classification of adverse events (AES) was confirmed by the National Cancer Institute Common Toxicity Standard (version 5.0) [13].

Outcome measures

(1) CR, PR, SD, PD and ORR were adopted to evaluate the difference of the best remission and the best objective remission rate between the two groups; (2) The difference of median PFS between the two groups was compared; (3) Subgroup analysis was conducted about the median PFS of patients with brain metastases and patients treated with trastuzumab for more than 6 months in the two groups; (4) Influencing factors of PFS were analyzed through univariate and multivariate Cox regression analysis; (5) The difference of adverse reactions incidence between the two groups was compared.

Statistical analysis

SPSS 23.0 was used to analyze the data. The enumeration data were expressed as cases (percentage; n, %), and were compared by chi square test or Fisher exact test; The age and ECOG scores of the patients in accordance with normal distribution were expressed as mean ± standard deviation ($\bar{x}$ ± sd) and the comparison between groups was conducted by independent sample t test using Bilateral α=0.05 as significant level; The Kaplan-Meier curves of PFS were drawn by GraphPad7.0 and compared by Log-rank test; Multivariate Cox regression analysis was used to evaluate the influencing factors of PFS; P<0.05 means that the difference is statistically significantly.

Results

Baseline data

Overall, visceral metastasis was found in more than 70% of the patients in the two groups and capecitabine was commonly used among all the combined chemotherapy drugs by most of the patients. There existed no significant differences in age, ECOG score or HR status between the two groups (P>0.05), but the utilization rate of some chemotherapy drugs had the differences (including navelbine, gemcitabine and taxanes); See **Table 1**.

Table 2. Remission of patients in two groups (n, %)

Groups	CR	PR	SD	PD	ORR (%)
Pyrotinib group (n=68)	9 (13.2)	32 (47.1)	21 (30.9)	6 (8.8)	41 (60.3)
Lapatinib group (n=96)	4 (4.2)	29 (30.2)	53 (55.2)	10 (10.4)	33 (34.4)
χ^2		12.492			10.799
P		0.005			0.001

Note: CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; ORR: objective response rate.

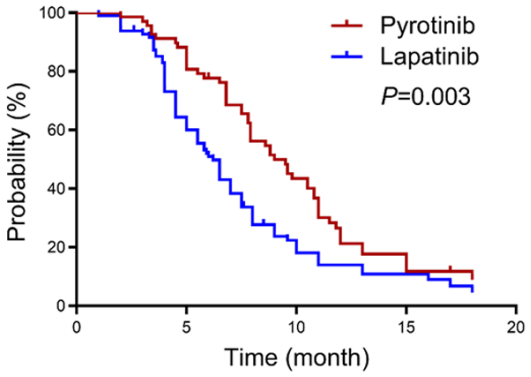

Figure 1. Kaplan-Meier curve of PFS in patients of two groups. PFS: progression free survival.

Comparison of the best response

In the pyrotinib group, 41 patients achieved objective remission (9 CR + 32 PR), with the best ORR of 60.3%; besides, 33 patients achieved objective remission (4 CR + 29 PR) in the lapatinib group, with the best ORR of 34.4% (**Table 2**). Thus, the pyrotinib group had much higher ORR than the lapatinib group (P<0.01).

Comparison of PFS

As can be seen from **Figure 1**, the median PFS (9.0 months vs. 6.2 months) in the pyrotinib group was significantly longer than that in the lapatinib group (HR=0.584, 95% CI: 0.411-0.829).

Subgroup analysis of PFS for patients in two groups

As shown in **Figure 2**, the median PFS of the patients with brain metastases in the pyrotinib group was 6.5 months, and was much longer that in the lapatinib group of 3.5 months (HR=0.433, 95% CI: 0.203-0.923); in patients treated with trastuzumab for more than 6 months, the median PFS in the pyrotinib group was significantly higher than that in the lapatinib group (11 months vs. 7.5 months; HR=0.478, 95% CI: 0.243-0.940).

COX regression analysis about influencing factors of PFS

Through univariate COX regression analysis, some variables related to PFS were revealed, including pyrotinib treatment, combined capecitabine treatment, hormone status, the number of metastatic sites, brain metastases and trastuzumab treatment ≥6 months (**Table 3**). These above variables were further analyzed by multivariate COX regression analysis. After other potential confounding factors were controlled, the results exhibited that pyrotinib treatment (HR=0.653), capecitabine treatment (HR=0.702), hormonal status (HR=0.750) and trastuzumab treatment ≥6 months (HR=0.725) were all associated with longer PFS (P<0.05), and brain metastasis (HR=1.365) was associated with shorter PFS (P<0.05). See **Table 4**.

Analysis of adverse reactions

Safety evaluation was conducted on 65 patients in the pyrotinib group and 90 patients in the lapatinib group. The incidence of diarrhea in the two groups was both pretty high, and diarrhea occurred in more than 80% of the patients in the pyrotinib group. However, the incidence concentrated in grade 1-2, and there existed no significant difference between the two groups. Besides, the lapatinib group had much higher proportion of vomiting and hand-foot syndrome than the pyrotinib group (P<0.05). Other adverse reactions included anemia, neutropenia, thrombocytopenia, rash, fatigue and elevated transaminase also occurred. See **Table 5**.

Discussion

This retrospective study pointed out that pyrotinib combined with chemotherapy showed significant efficacy in patients with HER2 positive advanced breast cancer who failed the first-line trastuzumab therapy. The results showed that the best ORR reached 60.3% in the pyrotinib group, and the median PFS was up to 9 months. Compared with the current lapatinib combined

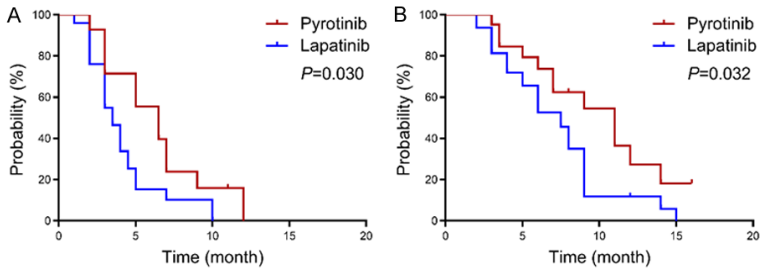

Figure 2. PFS subgroup analysis of patients in two groups. A: Kaplan-Meier curve of PFS in patients with midbrain metastasis in two groups (χ^2=4.692, Log-rank P=0.030); B: Kaplan-Meier curve of PFS in patients treated with trastuzumab for more than 6 months in both groups (χ^2=4.579, Log-rank P=0.033). PFS: progression free survival.

with chemotherapy (ORR of 34.4%, median PFS of 6.2 months), the efficacy in this present study has been further improved. However, compared with previous phase II and phase III clinical studies, the ORR of the pyrotinib regimen in this present study was relatively low, which was possibly related to the influence of baseline characteristics of the selected patients and complexity of combined chemotherapy drugs [10, 11].

NCCN guidelines list several treatment options for patients with HER-2 positive advanced breast cancer who have failed first-line treatment with trastuzumab [14]. These strategies include regimen containing lapatinib, continuous administration of trastuzumab as well as other chemotherapy drugs, termination of chemotherapy and combined application of trastuzumab and lapatinib dual targeted therapy, and the administration of TDM1. However, TDM1 is still not available in China, and dual targeting therapy is not suitable for most patients. In addition, most patients are not able to afford the expensive anti HER-2 drugs. As an anti HER-2 targeted drug independently developed in China, pyrotinib not only has price advantages, but also shows more benefit for patients [15, 16]. Therefore, for the majority of Chinese patients with HER2 positive advanced breast cancer who failed first-line treatment with trastuzumab, pyrotinib combined with chemotherapy is most likely the new ideal treatment option.

In subgroup analysis, we further showed that pyrotinib regimen had a significant advantage in the treatment of patients with brain metastases. Although Shawky et al. had previously showed that lapatinib combined with chemotherapy was effective in the treatment of breast cancer with brain metastasis [17]. The PFS of the pyrotinib group (6.5 months vs. 3.5 months) was significantly increased compared with that of the lapatinib group. Similar to the results of previous studies, our study suggests that pyrotinib may be a new option for patients with brain metastases [18, 19]. In addition, pyrotinib combined with chemotherapy also achieved a longer median PFS (11 months vs. 7.5 months) in patients treated with trastuzumab for more than 6 months, which further indicated that the pyrotinib regimen had more advantages for Chinese breast cancer patients.

Through the multivariate COX regression analysis, we found that capecitabine treatment (HR=0.702) was associated with longer PFS, which conforms to the results of previous studies [20, 21]. Therefore, capecitabine can be used as an ideal selection in the combination chemotherapy of pyrotinib. Positive hormone status (HR=0.750) is also an influencing factor of PFS. It is believed that patients with positive hormone status are mostly premenopausal, so they may have better physiological conditions and younger age [22, 23]. Brain metastasis (HR=1.365) is associated with shortened PFS, which is consistent with the conclusion of most studies [24, 25]. However, further studies are needed regarding pyrotinib regimen in the treatment for patients with brain metastases.

In terms of safety, pyrotinib and lapatinib had similar high incidence of diarrhea (81.5%, 72.2%), but the incidence of grade 3-4 diarrhea was lower comparatively. In addition, fewer vomiting and hand foot syndrome were observed in the pyrotinib group, presumably because pyrotinib is an irreversible tyrosine kinase inhibitor, which is related to the different mechanism of lapatinib [16]. The adverse reactions of pyrotinib and lapatinib were both acceptable essentially.

There are also several limitations in this study. Firstly, this is a retrospective study without pro-

Table 3. COX regression analysis about influencing factors of PFS in patients

Variables	HR	95% CI	P
Age (≤45 years old vs. >45 years old)	0.932	0.659-1.103	0.096
ECOG scores (scores)	1.085	0.809-1.303	0.088
Pyrotinib treatment (yes vs. no)	0.612	0.489-0.895	0.005
Capecitabine treatment (yes vs. no)	0.680	0.567-0.904	0.010
Hormonal status (positive vs. negative)	0.705	0.595-0.930	0.012
Number of transfer sites (≤2 vs. >2)	0.955	0.730-1.108	0.296
Brain metastasis (yes vs. no)	1.425	1.138-1.502	0.022
Visceral metastasis (yes vs. no)	1.106	0.986-1.423	0.095
Trastuzumab treatment ≥6 months (yes vs. no)	0.683	0.556-0.904	0.010

Note: HR: hormone; CI: Cardiac Index.

Table 4. Multivariate COX regression analysis about influencing factors of PFS in patients

Variables	HR	95% CI	P
Pyrotinib treatment (yes vs. no)	0.653	0.509-0.903	0.003
Capecitabine treatment (yes vs. no)	0.702	0.592-0.936	0.013
Hormonal status (positive vs. negative)	0.750	0.601-0.950	0.009
Number of transfer sites (≤2 vs. >2)	0.993	0.768-1.165	0.306
Brain metastasis (yes vs. no)	1.365	1.116-1.492	0.016
Trastuzumab treatment ≥6 months (yes vs. no)	0.725	0.619-0.955	0.020

Note: HR: hormone; CI: Cardiac index.

Table 5. Adverse reactions of patients in two groups (n, %)

Items	Pyrotinib group (n=65)		Lapatinib group (n=90)		χ^2	P*
	Total amount	Grade 3-4	Total amount	Grade 3-4		
Adverse reactions of digestive tract						
Diarrhea	53 (81.5)	9 (13.8)	65 (72.2)	11 (12.2)	1.803	0.179
Nausea	8 (12.3)	0 (0.0)	23 (25.6)	3 (3.3)	3.562	0.059
Vomiting	6 (9.23)	0 (0.0)	22 (24.4)	4 (4.4)	5.902	0.015
Hematological adverse reactions						
Anemia	11 (16.9)	0 (0.0)	10 (11.1)	0 (0.0)	1.088	0.297
Neutropenia	8 (12.3)	2 (1.5)	16 (17.8)	3 (3.3)	0.863	0.353
Thrombocytopenia	4 (6.2)	0 (0.0)	9 (10.0)	1 (1.1)	0.727	0.394
Other adverse reactions						
Rash	8 (12.3)	0 (0.0)	5 (5.6)	0 (0.0)	2.239	0.135
Fatigue	7 (10.8)	0 (0.0)	9 (10.0)	0 (0.0)	0.024	0.877
Hand-foot syndrome	13 (20.0)	2 (3.1)	42 (46.7)	14 (15.6)	11.724	0.001
Elevated transaminase	14 (21.5)	1 (1.5)	12 (13.3)	0 (0.0)	1.820	0.177

Note: *Comparison of the total incidence of AEs between the two groups.

spective randomized grouping. Therefore, there may exist a large bias in the sociological characteristics, physiological status, tumor characteristics and other baseline characteristics of patients, especially in the number of combined chemotherapeutic drugs between the two groups. In addition, multiple tests may increase the risk of type I errors when 0.05 was used as the statistical significance level standard in the retrospective studies.

In summary, for the Chinese patients experienced the failure of trastuzumab first-line treatment, especially the patients with brain metas-

tasis, pyrotinib combined with chemotherapy has more significant advantages in improving the clinical efficacy. However, there still lacks sufficient clinical data of pyrotinib, and it is necessary to conduct a larger sample size research with longer follow-up so as to explore its real efficacy and safety.

Disclosure of conflict of interest

None.

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