Pyrotinib In The Treatment of Women With Advanced HER2- Positive Breast Cancer: A Multicenter, Prospective, Real-World Study

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Abstract

Background: HER2-positive breast cancer was aggressive, resulting in a poorer prognosis. This multicenter study analyzed the real-world data of women treated with pyrotinib-based therapy, aiming to describe their characteristics, treatment regimens, and to investigate the clinical outcomes.

Patients and Methods: A total of 141 patients with HER2-positive breast cancer were enrolled from February 2019 to April 2020. Last follow-up time was February 2021. All patients were treated with pyrotinib-based therapy in 21-day cycles. The primary endpoint was progression-free survival (PFS).

Results: The median PFS (mPFS) for pyrotinib-based therapy was 12.0 months (95% CI 8.1-17.8) in all patients. Among the 44 patients with liver metastases, mPFS was 8.7 months (95%CI 6.3-15.4), compared to 12.3 months (95%CI 8.8-23.3) for the 97 patients without liver metastases ($P=0.172$). In addition, patients receiving pyrotinib-based therapy as their >2 lines treatment had a numerically lower mPFS than those receiving pyrotinib-based therapy as their ≤ 2 lines treatment (8.4 vs. 15.1 months, $P=0.107$). The mPFS was 12.2 months (95%CI 7.9-18.8) in patients with previous exposure to trastuzumab and 11.8 months (95%CI 6.8-22.9) in patients without previous exposure to trastuzumab ($P=0.732$). Moreover, mPFS in patients receiving regimens with and without capecitabine were 15.1 months (95%CI 10.0-18.8) and 8.4 months (95%CI 6.7-22.9), respectively ($P=0.070$). Furthermore, in patients with brain metastases, estimated 6-month PFS rate was 70.0%, and rate at 12 months was 60.0%. Seventy patients with measurable lesions were evaluable for response. The ORR was 38.57% and DCR was 85.71%. Most common adverse event was diarrhea (85.04%).

Conclusion: Pyrotinib-based therapy showed promising efficacy in patients with HER2-positive breast cancer and was well tolerated, especially in patients treated with pyrotinib as ≤ 2 lines treatment and receiving regimens with capecitabine. The results of the real-world study further confirmed the intriguing efficacy of pyrotinib.

Introduction

Breast cancer is one of the most commonly diagnosed malignancy worldwide. Due to lifestyle changes, the incidence of breast cancer is rising in women [1]. With the development of early detection and efficient therapies, mortality from breast cancer has decreased. Nevertheless, breast cancer remains an important cause of death [2, 3]. Human epidermal growth factor receptor 2 (HER2)-positive is a key oncogenic driver event, with pathogenesis mainly being the activation of the PI3K/Akt and MAPK pathways [4]. Overexpression of human epidermal growth factor receptor 2 (HER2) occurs in 15%-20% of breast cancer [5].

HER2-positive breast cancer was aggressive, resulting in a poorer prognosis [6, 7]. The anti-HER2 agents, such as trastuzumab, pertuzumab, lapatinib, and adotrastuzumab emtansine (TDM1), have dramatically improved the survival in patients with HER2-positive breast cancer [8, 9]. However, drug resistance remains a major challenge [10, 11]. Thus, the continued development of novel therapies is required.

Pyrotinib is a newly-developed irreversible pan-ErbB receptor tyrosine kinase inhibitor inhibiting HER1, HER2, and HER4 [12]. In an open-label phase II study, pyrotinib plus capecitabine had significantly longer progression-free survival (PFS) (18.1 months vs. 7.0 months, $p < 0.001$) and higher objective response rate (ORR) (78.5% vs. 57.1%, $p < 0.05$) than lapatinib plus capecitabine in patients with HER2+ breast cancer [13]. In addition, a randomized Phase III trial (PHOEBE) enrolled 267 patients previously treated with trastuzumab. The results showed that median PFS was significantly longer in patients receiving pyrotinib plus capecitabine than in those receiving lapatinib plus capecitabine (12.5 months vs 6.8 months, $P < 0.0001$), and objective response rate (ORR) was higher for patients treated with pyrotinib plus capecitabine than those treated with lapatinib plus capecitabine (67.2% vs 51.5%). The most common adverse event was diarrhea which was well manageable [14]. Several randomized trials showed the promising efficacy of pyrotinib in HER2+ breast cancer. However, the efficacy of pyrotinib in patients with different baseline characteristics in the actual clinical practice was rarely reported.

This multicenter study analyzed the real-world data of women treated with pyrotinib-based therapy, aiming to describe their characteristics, treatment regimens, and to investigate the clinical outcomes.

Patients And Methods

Study Design, Treatment, and Assessment

This was a multicenter, prospective, real-world study conducted at 15 hospitals in China. A total of 141 patients with HER2-positive breast cancer were enrolled from February 2019 to April 2020. Last follow-up time was February 2021. All patients were treated with pyrotinib-based therapy in 21-day cycles. Starting dose was determined by physicians' choice and collected in the Case Report Form (CRF). This study was approved by the Ethics Board of Jiangsu Cancer Hospital (No. 2019-019) and performed in accordance with the Declaration of Helsinki. Written informed consents were obtained from all patients. This trial was registered with Chinese Clinical Trial Registry (ChiCTR1900021819, 11/3/2019).

Patient Population

Patients were eligible if they were aged ≥ 18 years and pathologically confirmed advanced HER2-positive breast cancer. HER2 status was evaluated on the basis of ASCO/CAP guidelines [15]. Patients were excluded if they (i) were pregnant or breastfeeding, (ii) had been previously treated with pyrotinib, (iii) lost information of treatment, (iv) received less than one cycle of treatment with pyrotinib. No limits on prior therapy were required.

Study End Points

The primary endpoint was progression-free survival (PFS), which was calculated as the time from the beginning of treatment with pyrotinib to confirmed disease progression or death. The secondary endpoint included objective response rate (ORR), and disease control rate (DCR) and overall survival (OS). Tumor response assessments were conducted according to Response Evaluation Criteria in Solid Tumors

(RECIST, version 1.1). Safety assessments were performed using Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Statistical Analyses

Patient characteristics, treatment regimens and starting dosages of pyrotinib were summarized as frequency count (percentage) or median (range). Median PFS was tested by the Kaplan–Meier method. Analyses were performed using STATA statistical software version 15.1 or MedCalc version 18.2.1. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 141 patients were included from February 2019 to April 2020. Baseline characteristics were showed in Table 1. Median age was 52 (range 29–78 years). One hundred and thirty-six patients (96.45%) had Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2 . Hormone receptor (HR)-positive was present in 56.03 % of the patients. The metastatic sites were in brain (14.89%), liver (31.21%), bone (43.97%) and lung (54.61%). Trastuzumab was previously administered in the (neo)adjuvant setting, metastatic setting, and both (neo)adjuvant setting and metastatic setting to 54(43.55%), 88(70.97%), and 18(14.52%) patients, respectively. Patients with primary trastuzumab-resistant breast cancer was 12.10% (Table1).

Treatment administration

One hundred and four (73.76%) patients received pyrotinib-based therapy as the second or further line of treatment (Table 2). One hundred (70.92%) patients initiated pyrotinib treatment at 400 mg. Thirty-nine (27.66%) patients started with 320 mg, and 2 (1.42%) patients had a starting dose of 160mg (Table 2). The patients received the treatment regimens with capecitabine (55.32%), trastuzumab (17.73%), and endocrine therapy, radiotherapy or antiangiogenic drugs (3.55%) (Table 2). Only 11 (7.80%) patients were treated with single agent (Table 2).

Efficacy

At the time of analysis in February 2021, fifty-eight (41.13%) patients were still receiving pyrotinib. The median PFS (mPFS) for pyrotinib-based therapy was 12.0 months (95% CI 8.1-17.8) in all patients (Figure 1). Subgroup analyses were conducted according to brain metastasis, liver metastasis, the lines of systematic therapy of pyrotinib, prior exposure to trastuzumab, and regimen with capecitabine. Among the 44 patients with liver metastases, mPFS was 8.7 months (95%CI 6.3-15.4), compared to 12.3 months (95%CI 8.8-23.3) for the 97 patients without liver metastases ($P = 0.172$) (Figure 2). In addition, patients receiving pyrotinib-based therapy as their >2 lines treatment had a numerically lower mPFS than those receiving pyrotinib-based therapy as their ≤ 2 lines treatment (8.4 vs. 15.1 months, $P = 0.107$) (Figure 3). The mPFS was 12.2 months (95%CI 7.9-18.8) in patients with previous exposure to trastuzumab and 11.8

months (95%CI 6.8-22.9) in patients without previous exposure to trastuzumab ($P=0.732$) (Figure 4). Moreover, mPFS in patients receiving regimens with and without capecitabine were 15.1 months (95%CI 10.0-18.8) and 8.4 months (95%CI 6.7-22.9), respectively ($P=0.070$) (Figure 5). Furthermore, in patients with brain metastases, estimated 6-month PFS rate was 70.0%, and rate at 12 months was 60.0% (Figure 6). As of data cutoff, mOS has not yet been reached.

Seventy patients with measurable lesions were evaluable for response. The ORR was 38.57% and DCR was 85.71%. 1 (1.43%) patient achieved complete response (CR) and 26 (37.14%) patients had partial response (PR). Thirty-three (47.14%) patients achieved stable disease (SD) and 10 (14.29%) patients had progression disease (PD) (Table 3). Subgroup analyses based on brain metastasis, liver metastasis, the lines of systematic therapy of pyrotinib, prior exposure to trastuzumab, and regimen with capecitabine are shown in Table 4.

Safety

One hundred and twenty-seven patients were included in the safety assessments. The adverse events (AEs) of all grades and grade ≥ 3 were reported in 123 patients (96.85%) and 14 patients (11.02%), respectively (Table 5). The most common AE was diarrhea (85.04%), but only 6 patients (4.72%) reported Grade ≥ 3 diarrhea. Moreover, the AEs of all grades that were documented in $\geq 15\%$ of patients included anemia (37.01%), leukopenia (24.6%), vomiting (24.41%), neutropenia (22.22%), and hyperbilirubinemia (17.32%). No treatment-related deaths were reported. Overall, the safety of pyrotinib-based therapy was controllable and tolerable.

Discussion

HER2-positive breast cancer is a more aggressive phenotype [16]. The anti-HER2 agents (trastuzumab, pertuzumab, lapatinib, and TDM1) have dramatically improved the prognosis in patients with HER2-positive breast cancer [17]. However, primary or acquired resistance to anti-HER2 agents remains a major challenge [10]. Thus, the novel therapy is required to provide option to patients.

This study was carried out to analyze the efficacy and safety of pyrotinib-based therapy in patients with HER2-positive breast cancer in the real world. The most inspiring result of the study was a mPFS of 12.0 months, higher than that of trastuzumab (10.9 months) and TDM1 (10.0 months) in real-world setting [18, 19], and close to the mPFS result (12.5 months) of pyrotinib in previous phase III trial (PHOEBE) [14]. In addition, the ORR of pyrotinib-based therapy in this study was 38.57% was also superior to that of TDM1 (20.0%) [20].

Subgroup results confirmed that the mPFS in patients with liver metastases was 8.7 months, which was shorter than the 12.3 months found in patients without liver metastases. This result is concordant with previous report in which liver metastases correlated with worse survival in patients with breast cancer [21,22]. Moreover, the mPFS was 15.1 months in patients receiving pyrotinib as ≤ 2 lines treatment, similar to the result of trastuzumab as first-line treatment reported in PUFFIN study (14.5 months) [23].

Our study demonstrated the efficacy of pyrotinib, providing evidence for the patients treated with pyrotinib as ≤ 2 lines treatment. In addition, 87.94% patients in our study received prior trastuzumab treatment, thus we assessed the benefit of pyrotinib-based therapy in patients progressed on trastuzumab. The results showed that patients could benefit from pyrotinib, regardless of whether they had been previously exposed to trastuzumab or not. Our results also confirmed that pyrotinib-based therapy with capecitabine achieved a numerically higher ORR and longer mPFS than that without capecitabine, which merits further assessment in the future. In addition, among patients with brain metastases, the 6-month and 12-month PFS rates were 70.0% and 60.0%, respectively, numerically better than that of anti-HER2 monoclonal antibodies in patients with brain metastases [18, 24, 25], indicating that pyrotinib is an important treatment option for patients with brain metastases.

Diarrhea was the most common AE (85.04%), but only 4.72% patients were reported grade ≥ 3 diarrhea which could be well controlled. The incidence of diarrhea in our study was lower than that in previously studies of pyrotinib [14, 26], which may be the result of the relatively low dose of pyrotinib (only 70.92% of patients were treated with pyrotinib at a starting dose of 400 mg/day). The antidiarrhea treatment or dose reduction after diarrhea could well control the occurrence of diarrhea.

This study confirmed the advantages of pyrotinib. However, the data were acquired from an observational study which included potential information bias or incomplete data. In addition, mOS has not yet been reached. Despite these limitations, the results of this study provide evidence for the real-world use of pyrotinib in patients with HER2-positive breast cancer.

In conclusion, pyrotinib-based therapy showed promising efficacy in patients with HER2-positive breast cancer and was well tolerated, especially in patients treated with pyrotinib as ≤ 2 lines treatment and receiving regimens with capecitabine. The results of the real-world study further confirmed the intriguing efficacy of pyrotinib.

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Tables

Table 1. Patient characteristics at baseline

Characteristic	No. of patients (%) (n=141)
Age, median (range, yr)	52(29-78)
ECOG performance status	
<2	136(96.45)
≥2	5(3.55)
Hormone receptor status	
HR positive	79(56.03)
HR negative	61(43.26)
Unknown	1(0.71)
Metastatic sites	
Brian	21(14.89)
Liver	44(31.21)
Bone	62(43.97)
Lung	77(54.61)
Previous trastuzumab therapy	124(87.94)
For advanced disease	88(70.97)
As neo/adjuvant therapy	54(43.55)
Both	18(14.52)
Primary resistance to trastuzumab*	15(12.10)

*Primary resistance to trastuzumab was defined as relapse during or within 12 months after adjuvant trastuzumab or progression within 3 months of trastuzumab treatment for metastatic disease.

Table 2. Treatment administration

Pyrotinib treatment	No. of patients (%) (n=141)
Lines of systematic therapy of pyrotinib for ABC/MBC	
1	37(26.24)
≥2	104(73.76)
Starting dosage of Pyrotinib (mg/day)	
400mg	100(70.92)
320mg	39(27.66)
160mg	2(1.42)
Regimens	
Regimens with capecitabine	78(55.32)
Pyrotinib + capetabine	69(88.46)
Pyrotinib + capetabine + paclitaxel	1(1.28)
Pyrotinib + capetabine + trastuzumab	8(10.26)
Regimens with trastuzumab	25(17.73)
Pyrotinib + trastuzumab + chemotherapy	18(72.00)
Pyrotinib + trastuzumab + pertuzumab + chemotherapy	1(4.00)
Pyrotinib + trastuzumab	4(16.00)
Pyrotinib + trastuzumab + endocrine therapy	2(8.00)
Pyrotinib	11(7.80)
Pyrotinib + endocrine therapy	2(1.42)
Pyrotinib + radiotherapy	2(1.42)
Pyrotinib + antiangiogenic drug	1(0.71)

Abbreviations: ABC, advanced breast cancer; MBC, metastatic breast cancer.

Table 3. Objective response rate in 70 patients with measurable lesions at baseline

Best response	No. of patients (%) (n=70)
CR	1(1.43)
PR	26(37.14)
SD	33(47.14)
PD	10(14.29)
ORR	27(38.57)
DCR	60(85.71)

Table 4. The subgroup analyses of the objective response rate

Best response	ORR (%)	DCR (%)
Brain metastasis		
Yes	45.45	90.91
No	37.29	84.75
Liver metastasis		
Yes	39.13	86.96
No	38.30	85.11
Lines of systematic therapy of pyrotinib		
>2	32.35	79.41
≤2	44.44	91.67
Prior exposure to trastuzumab		
Yes	36.07	85.25
No	50.00	87.50
Regimen with capecitabine		
Yes	35.29	85.29
No	33.33	86.67

Table 5. Adverse events

Adverse event	All Grade	Grade $\geq$ 3
Diarrhea	85.04%	4.72%
Anemia	37.01%	0.00%
Leukopenia	24.60%	0.00%
Vomiting	24.41%	0.79%
Neutropenia	22.22%	2.38%
Hyperbilirubinemia	17.32%	3.15%
Aspartate aminotransferase increased	11.81%	0.79%
Alkaline phosphatase increased	11.81%	0.79%
γ -glutamyltransferase increased	11.02%	1.58%
Thrombocytopenia	9.52%	0.00%
Rash	9.45%	1.57%
Hypoalbuminemia	9.45%	0.79%
Alanine aminotransferase increased	9.45%	0.00%
Nausea	7.87%	0.00%
Asthenia	5.51%	0.00%
Stomatitis	4.72%	0.00%
Decreased appetite	4.72%	0.00%
Hand-foot syndrome	1.57%	0.00%
Paronychia	1.57%	0.00%
Kidney function abnormalities	1.57%	0.00%
Abdominal pain	0.79%	0.00%
Palpitation	0.79%	0.00%
Dizziness	0.79%	0.00%
Pruritus	0.79%	0.00%

Figures

Figure 1

Kaplan-Meier estimates of PFS for all patients treated with pyrotinib-based therapy

Number at risk

Without liver metastases

97 73 44 19 11 3 0

With liver metastases

44 31 20 11 3 0 0

Figure 2

Kaplan-Meier estimates of PFS for patients with and with and without liver metastases

Number at risk							
≤ 2 lines							
	82	68	39	17	8	1	0
> 2 lines							
	59	36	25	13	6	2	0

Figure 3

Kaplan-Meier estimates of PFS for patients stratified by treatment lines

Figure 4

Kaplan-Meier estimates of PFS for patients with and without prior trastuzumab exposure

Number at risk						
Regimens without capecitabine						
63	41	22	11	4	0	0
Regimens with capecitabine						
78	63	42	19	10	3	0

Figure 5

Kaplan-Meier estimates of PFS for patients receiving regimens with and without capecitabine

Figure 6

Kaplan-Meier estimates of PFS for patients with brain metastases