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ORIGINAL ARTICLE

Efficacy of everolimus combined with endocrine therapy in HR-positive/HER-2-negative advanced breast cancer

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Summary

Purpose: *To explore the efficacy and safety of everolimus combined with endocrine therapy in patients with hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER-2)-negative advanced breast cancer.*

Methods: *The clinical information of 108 patients with HR-positive/HER-2-negative advanced breast cancer, who were admitted to and treated in our hospital from June 2014 to June 2016, was retrospectively analyzed. Of them, 54 patients were treated with everolimus combined with endocrine drugs (Everolimus group), while the other 54 patients underwent endocrine monotherapy (Control group). The clinical response rate and incidence of adverse reactions were compared between the two groups of patients, and the patients were followed up to record survival. Besides, the possible influencing factors for progression-free survival (PFS) were analyzed.*

Results: *The objective response rate (ORR) was 22.2% and 14.8%, respectively, in everolimus group and the Control group, while the clinical benefit rate (CBR) was 66.7% and 37.0%, respectively, in the two groups. There were statistically significant differences in the CBRs of the first-line and second-line therapies. The majority of adverse reactions were in grade I and II, with lower incidence rates of grade III and IV adverse reactions. The median PFS of the two groups of patients was 7.3±5.6 months and 6.7±5.1 months, respectively. The log-rank test revealed that there was a statistically significant difference in the PFS between the two groups of patients. According to the multivariate regression analysis results, progesterone receptor (PR)$^+$, absence of visceral metastases, and sensitivity to endocrine therapy were the protective prognostic factors for PFS.*

Conclusion: *Everolimus combined with endocrine therapy has significant clinical efficacy in patients with HR-positive/HER-2-negative advanced breast cancer, and can effectively improve the survival of patients with tolerable adverse reactions. PR$^+$, absence of visceral metastases and sensitivity to endocrine therapy are the protective prognostic factors for PFS.*

Key words: *everolimus, endocrine therapy, breast cancer, advanced stage, hormone receptor, human epidermal growth factor receptor-2*

Introduction

Breast cancer ranks first among malignancies in females in terms of morbidity, and is a major cause of deaths in women. As reported in the global cancer statistics in 2012, there are approximately 1.7 million women suffering from breast cancer worldwide each year [1]. The cases of hormone receptor (HR)-positive breast cancer represent about 75% of the total. It has been recommended jointly in several consensus guidelines that endocrine therapy is preferred for HR-positive advanced

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breast cancer patients with only bone/soft tissue metastases or asymptomatic visceral metastasis [2,3]. However, nearly 30% of patients with HR-positive breast cancer develop primary resistance to endocrine therapy, whereas about 40% of patients previously sensitive to endocrine therapy experience secondary resistance [4].

Recent studies have found that the resistance to endocrine therapy is associated with the activation of several growth factor signaling pathways, especially the estrogen receptor (ER) signaling pathway and the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway [5-7]. Currently, the large-scale clinical research into the inhibitors of the PI3K/Akt/mTOR pathway-associated targets has been extensively performed in HR-positive advanced breast cancer. Everolimus, the mTOR inhibitor, has already been approved by the U.S. FDA in 2012 to be applied in postmenopausal patients with HR-positive/ human epidermal growth factor receptor 2 (HER-2)-negative advanced breast cancer, providing a novel idea for the options of clinical regimens after the patients with HR-positive advanced breast cancer are resistant to endocrine therapy [8,9]. The present study retrospectively analyzed the clinical information of 108 HR-positive and HER-2-negative patients with advanced breast cancer who were admitted to and treated in our hospital from June 2014 to June 2016, to explore the efficacy and safety of everolimus combined with endocrine therapy in treating patients with HR-positive /HER-2-negative advanced breast cancer, with the hope of providing a basis for the formulation of clinical strategies to treat such patients.

Methods

General information

The clinical information of 108 HR-positive/HER-2-negative advanced breast cancer patients admitted to and treated in our hospital from June 2014 to June 2016 was collected based on the following criteria.

Inclusion criteria: patients aged ≥18 years old, those pathologically diagnosed with locally recurrent or distantly metastatic advanced breast cancer, HR-positive/HER-2-negative patients as indicated by immunohistochemical tests, those treated using multi-line rescue therapies, those with measurable or assessable lesions, and those scoring 0-2 points based on the Eastern Cooperative Oncology Group scale.

Exclusion criteria: patients with severe dysfunction of the liver, kidney or other solid organs, those complicated with endocrine system-associated diseases such as hyperthyroidism and diabetes, those who were newly diagnosed with unresectable locally advanced or metastatic breast cancer and planned to undergo first-line rescue therapy, those previously treated with everolimus, or those with predicted survival time <3 months.

All the patients were treated based on different regimens: everolimus combined with endocrine medications (Everolimus group, n=54) and endocrine monotherapy (Control group, n=54). There were no differences in the general clinical baseline data between the two groups of patients ($p>0.05$), which were comparable in the baseline (Table 1). All the enrolled patients followed the Declaration of Helsinki, and they were informed of this study and signed the informed consent form. This study was approved by the Ethics Committee of Jiyang People's Hospital.

Treatment methods

Everolimus group (n=54): Everolimus was administered daily once at an initial dose of 10 mg and at the adjusted dose of 5 mg based on adverse reactions. There were 21 cases taking the combined exemestane (25 mg q.d.), 5 cases taking the combined letrozole (2.5 mg q.d.) and anastrozole (1 mg q.d.), and 3 cases taking the combined tamoxifen (10 mg q.d.) and toremifene (60 mg q.d.). Besides, the patients gargled using dilute brine to prevent oral ulcers, and those with bone metastasis were given bisphosphonates monthly to protect bones.

Control group (n=54): The patients were administered equal doses of the above endocrine drugs.

Observation indicators

Prior to treatments, all the patients had baseline imaging examinations and underwent imaging assessment once every 2-3 months based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1: complete response (CR): Disappearance of all target lesions for at least 4 weeks; partial response (PR): At least 30% decrease in the sum of the longest diameter of target lesions for at least 4 weeks, with the sum of longest diameter as the reference; progressive disease (PD): At least 20% increase in the sum of the longest diameter of target lesions, or the appearance of one or more new lesions; stable disease (SD): Neither sufficient decrease in the sum of the longest diameter of lesions to PR nor sufficient increase to PD. Objective response rate (ORR) =CR+PR, and clinical benefit rate (CBR) =CR+PR+SD.

Adverse reactions were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events 4.0.

Follow-up was conducted at 1, 3, 6 and 12 months after treatment and subsequently every 3-6 months until June 2019, during which the survival of patients was recorded. Progression-free survival (PFS) is defined as the duration of time from the beginning of treatment to the onset of PD or death of any cause, while overall survival (OS) as the duration of time from the date of chemotherapy to the day of death or the last follow-up date. Univariate analyses were conducted on the possible factors affecting patient prognosis, and the indicators showing statistically significant differences were included into the Cox proportional hazards model for multivariate analyses.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean±standard deviation and intergroup comparisons were made using pairwise t-test. Enumeration data were presented as ratios (%), and x^2 test was performed for intergroup comparisons. The survival curves were plotted using Kaplan-Meier method. Log-rank test was performed to verify whether the difference in the survival rate between the two groups was statistically significant, and $p<0.05$ suggested statistically significant difference.

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	*Everolimus group (n=54) n (%)*	*Control group (n=54) n (%)*	*p value*
Age, years	51.34±9.82	53.03±9.81	0.373
Pathological type			0.728
Invasive ductal carcinoma	41 (75.9)	44 (81.5)	
Invasive lobular carcinoma	7 (13.0)	5 (9.3)	
Invasive poorly differentiated adenocarcinoma	2 (3.7)	3 (5.6)	
Medullary carcinoma	4 (7.4)	2 (3.7)	
Menstrual status			0.448
Premenopausal	11 (20.4)	8 (14.8)	
Postmenopausal	43 (79.6)	46 (85.2)	
ER			0.483
+	24 (44.4)	18 (33.3)	
++	10 (18.5)	13 (24.1)	
+++	20 (37.1)	23 (42.6)	
PR			0.355
+	40 (74.1)	44 (81.5)	
-	14 (25.9)	10 (18.5)	
Molecular subtyping			0.870
Luminal A	17 (31.5)	14 (25.9)	
Luminal B Her-2 (-)	26 (48.1)	29 (53.7)	
Luminal B Her-2 (+)	8 (14.8)	9 (16.7)	
Not clear	3 (5.6)	2 (3.7)	
Number of metastatic lesions			0.564
<3	25 (46.3)	28 (51.9)	
≥3	29 (53.7)	26 (48.1)	
Visceral metastasis			0.562
Yes	32	28	
No	22	26	
Previous treatment			0.266
First-line	20 (37.0)	17 (31.5)	
Second-line	18 (33.3)	13 (24.1)	
Third-line or more	16 (29.6)	24 (44.4)	
Previous sensitivity to endocrine therapy			0.557
Sensitive	34	30	
Insensitive	20	24	
Endocrine therapy drugs			0.825
Exemestane	38 (70.4)	35 (64.8)	
Letrozole/ Anastrozole	6 (11.1)	8 (14.8)	
Letrozole/ Goserelin	6 (11.1)	5 (9.3)	
Tamoxifen/ Toremifene	4 (7.4)	6 (11.1)	

ER: estrogen receptor; PR: progesterone receptor

Results

Comparison of clinical short-term efficacy between the two groups of patients

Upon completion of treatment, the efficacy was evaluated in all the patients. The mean of chemotherapy cycles was 5.7 in the Everolimus group and 3.4 in the Control group. The Everolimus group had no case of CR, 12 cases of PR (22.2%), 24 cases of SD (44.4%) and 18 cases of PD (33.3%), with ORR 22.2% (12) and CBR 66.7% (36). In the control group, there were no cases of CR, 8 cases of PR (14.8%), 12 cases of SD (22.2%), and 34 cases of PD (63.0%), and the ORR and CBR were 14.8% (8) and 37.0% (20), respectively. The difference in the ORR between the two groups was not statistically significant, but there was a statistically difference in the CBR between the two groups (p=0.322, p=0.019). Moreover, the ORR of the first-line therapy was 30.0% and 23.5%, respectively, in the two groups, showing no statistically significant difference (p=0.725), while the CBR was 85.0% and 64.7%, respectively, in the two groups, with statistically significant difference (p=0.025). The ORR of the second-line therapy was 22.2% and 15.4%, respectively, in the two groups, with no statistically significant difference (p=0.812), whereas the CBR was 50.0% and 30.8%, respectively, in the two groups, showing a statistically significant difference (p=0.036). The ORR of the third-line and later-line therapies was 18.8% and 8.3%, and the CBR was 25.0%, and 20.8%, respectively, in the two groups, with no statistically significant differences (p=0.179, p=0.530) (Table 2).

Comparison of incidence of adverse reactions between the two groups of patients

In the Everolimus group, except 2 cases of drug discontinuation for economic reasons, the prima-

Table 2. Clinical effective rates of the two studied groups

Clinical effective rates	*Everolimus group (n=54) n (%)*	*Control group (n=54) n (%)*	*p value*
Overall			
CR	0 (0)	0 (0)	
PR	12 (22.2)	8 (14.8)	
SD	18 (33.3)	12 (22.2)	
PD	24 (44.4)	34 (63.0)	
ORR	12 (22.2)	8 (14.8)	0.322
CBR	30 (55.5)	20 (37.0)	0.019
First-line			
CR	0 (0)	0 (0)	
PR	6 (30.0)	4 (23.5)	
SD	11 (55.0)	7 (41.2)	
PD	3 (15.0)	6 (35.3)	
ORR	6 (30.0)	4 (23.5)	0.725
CBR	17 (85.0)	11 (64.7)	0.025
Second-line			
CR	0 (0)	0 (0)	
PR	4 (22.2)	2 (15.4)	
SD	5 (27.8)	2 (15.4)	
PD	9 (50.0)	9 (69.2)	
ORR	4 (22.2)	2 (15.4)	0.812
CBR	9 (50.0)	4 (30.8)	0.036
Third-line or more			
CR	0 (0)	0 (0)	
PR	2 (18.8)	2 (8.3)	
SD	2 (18.8)	3 (12.5)	
PD	12 (75.0)	19 (79.2)	
ORR	2 (18.8)	2 (8.3)	0.179
CBR	4 (25.0)	5 (20.8)	0.530

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; CBR: clinical benefit rate

Table 3. Comparison of adverse reactions of patients in the two studied groups

Adverse effects	*Everolimus group (n=54)* *n (%)*	*Control group (n=54)* *n (%)*	*p value*
Fever	7 (13.0)	4 (7.4)	0.340
Fatigue	18 (33.3)	14 (25.9)	0.399
Skin rash	9 (16.7)	6 (11.1)	0.404
Bone marrow suppression	15 (27.8)	13 (24.1)	0.661
Nausea, vomiting	6 (11.1)	5 (9.3)	0.750
Diarrhea	4 (7.4)	6 (11.1)	0.507
Liver dysfunction	12 (22.2)	8 (14.8)	0.322
Renal dysfunction	3 (5.6)	1 (1.9)	0.308
Oral mucositis	50 (92.6)	9 (16.7)	0.001
Interstitial pneumonia	14 (25.9)	2(3.7)	0.001
Hyperglycemia	5 (9.3)	6 (11.1)	0.750
Perianal abscess	1 (1.9)	0 (0)	0.351

ry adverse reactions in the remaining 52 patients were as follows: oral mucositis (92.6%), fatigue (33.3%), interstitial pneumonia (25.9%), myelosuppression (27.8%), rash (16.7%), gastrointestinal reaction (18.5%), renal function impairment (22.2%), hyperglycemia (9.3%) and perianal abscess (1.9%). Grade I and II adverse reactions prevailed, while the incidence rates of grade III and IV were lower. The dosage of everolimus was adjusted to 5 mg/d for adverse reactions in 24 cases. Of them, 7 patients discontinued everolimus due to interstitial lung disease, and after the symptoms were mitigated using corticosteroids, they continued to be treated with everolimus at the reduced dose of 5 mg daily and showed tolerance. Besides, one patient underwent incision and drainage due to perianal abscess twice, and tolerated the everolimus reduced to 5 mg after symptom relief, one patient with severe interstitial pneumonia received active symptomatic treatment and discontinued everolimus because of intolerance to the everolimus at the reduced dose, after symptom improvement, and one patient discontinued the drug due to acute renal function impairment. There were no drug adverse reactions related deaths. The incidence rate of adverse reactions had no statistically significant difference between the two groups (p>0.05) (Table 3).

Follow-up results of patient survival

Up to June 2019, the mean follow-up time of the two groups of patients was 21.1±5.3 months and 20.4±5.0 months, respectively. In the follow-up, the Everolimus group and the Control group had 5 and 2 cases of stable disease, respectively, and the mean PFS (mPFS) of the two groups of patients was 7.3±5.6 months and 6.7±5.1 months, respectively.

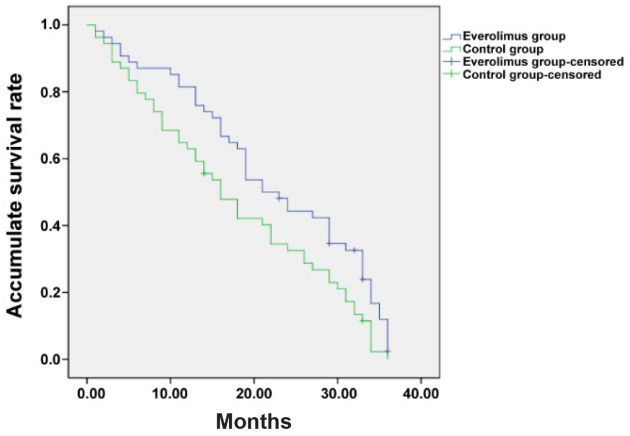

Figure 1. Kaplan-Meier survival curves of patients in the Everolimus group and the Control group. The progression-free survival rate of patients in the Everolimus group was significantly higher than that of patients in the Control group (p=0.015).

The survival curves of the two groups of patients were plotted using the Kaplan-Meier method, and the log-rank test results revealed that there was a statistically significant difference in the PFS between the two groups of patients (p=0.015) (Figure 1).

Analysis results of influencing factors for patient prognosis

The survival data were subjected to stratification analysis based on the possible factors for prognosis, and age, pathological type, menstrual status, ER, progesterone receptor (PR), molecular type of tumors, number of metastases, presence or absence of visceral metastases, previous sensitivity to endocrine therapies and type of the present endocrine drugs were included in univariate analysis. The results revealed that the presence or absence of visceral metastases and previously

being sensitive to endocrine affected the mPFS of patients. The mPFS of patients with no visceral metastases was obviously longer than that of patients with visceral metastases (11.1±4.2 months *vs.* 5.9±3.4 months) with statistically significant difference (p<0.001). The patients previously sensitive to endocrine therapy had distinctly longer mPFS than those previously insensitive to endocrine therapy (8.6±3.8 months *vs.* 4.8±3.2 months), showing a statistically significant difference (Table 4). According to the Cox multivariate analysis, the PFS was correlated with the presence or absence

Table 4. Univariate analysis of predictors for mPFS (months) in patients with advanced HR-positive HER-2 negative breast cancer

Parameters	*Cases*	*PFS (months)*	*p value*
Age (years)			0.116
≤50	56	6.8±3.9	
>50	62	8.0±4.3	
Pathological type			0.652
Invasive ductal carcinoma	85	6.9±3.6	
Invasive lobular carcinoma	12	9.8±3.4	
Invasive poorly differentiated adenocarcinoma	5	6.7±3.1	
Medullary carcinoma	6	6.5±3.0	
Menstrual status			0.336
Premenopausal	19	7.3±4.2	
Postmenopausal	89	6.6±3.6	
ER			0.429
+	42	5.8±3.8	
++	23	7.1±4.9	
+++	43	7.3±4.4	
PR			0.371
+	84	7.4±4.1	
-	24	5.7±3.3	
Molecular subtyping			0.277
Luminal A	31	5.9±3.1	
Luminal B Her-2 (-)	55	7.2±4.6	
Luminal B Her-2 (+)	17	5.3±4.9	
Not clear	5	7.8±4.0	
Number of metastatic lesions			0.755
<3	53	6.9±3.2	
≥3	55	7.3±4.6	
Visceral metastasis			0.001
Yes	60	5.9±3.4	
No	48	11.1±4.2	
Previous treatment			0.149
First-line	37	11.7±4.9	
Second-line	31	7.0±3.9	
Third-line or more	40	5.9±3.6	
Previous sensitivity to endocrine therapy			0.001
Sensitive	64	8.6±3.8	
Insensitive	44	4.8±3.2	
Endocrine therapy drugs			0.236
Exemestane	73	6.7±3.3	
Letrozole/ Anastrozole	14	9.0±4.1	
Letrozole/ Goserelin	11	5.1±3.6	
Tamoxifen/ Toremifene	10	8.4±4.1	

HR: hormone receptor; HER-2: human epidermal growth factor receptor-2; ER: estrogen receptor; PR: progesterone receptor; PFS: progression free survival

Table 5. Multivariable Cox regression analysis of predictors for advanced HR-positive HER-2 negative breast cancer patients

Parameters	*Hazard ratio*	*95% CI*	*p value*
PR	0.219	0.034-0.455	0.009
Visceral metastasis	0.067	0.021-0.250	0.001
Previous sensitivity to endocrine therapy	0.327	0.055-0.763	0.019

HR: hormone receptor; HER-2: human epidermal growth factor receptor-2; PR: progesterone receptor; CI: confidence interval

of visceral metastases, PR status and sensitivity to endocrine therapy. Among them, PR^+ [hazard ratio (HR)=0.219, p=0.009)], absence of visceral metastases (HR=0.067, p<0.001), and sensitivity to endocrine therapy (HR=0.327, p=0.019) were the protective prognostic factors for PFS (Table 5).

Discussion

As the treatment of advanced breast cancer is intended to improve symptoms, delay disease progression, prolong survival and raise quality of life, both the efficacy and the influence of treatment on the quality of life of patients are needed to be considered in terms of the selection of treatment regimens. Endocrine therapy is an optimal option for HR-positive slowly progressing breast cancer patients with only bone/soft tissue metastases or no visceral metastases, but its efficacy is influenced by endocrine resistance. Current studies have confirmed that the activation of the PI3K/Akt/mTOR pathway mediates the resistance of breast cancer to endocrine therapy, and that inhibiting this pathway-associated targets and resisting the relevant mutant genes in a targeted manner can restore or enhance the sensitivity to endocrine therapy, which is now the novel solution to the endocrine resistance. According to the results of several studies, everolimus, as a selective oral inhibitor of mTOR, achieves good efficacy in HR-positive breast cancer through combining with endocrine therapy and compared with endocrine drugs alone. Everolimus combined with endocrine therapy can prolong the mPFS of patients by 2.0-6.0 months, with tolerable adverse reactions [10-13].

In this study, the ORR and CBR were 22.2% and 66.7%, respectively, in the Everolimus group (n=54), and 14.8% and 37.0%, respectively, in the Control group (n=54). The difference in the ORR between the two groups was not statistically significant, but there was a statistically significant difference in the CBR between the two groups (p=0.322, p=0019). Besides, the differences in the ORRs of the first-line, second-line and third-line therapies between the two groups were not statistically significant (p>0.05), while there were statistically significant differences in the CBRs of the first-line and second-line therapies (p<0.05), but not in the CBRs of the third-line and later-line therapies (p>0.05). The results of studies in China and beyond have demonstrated that the ORR and CBR of everolimus combined with endocrine therapy are 6.3-26.7% and 22.9-61%, respectively, in the advanced HR-positive breast cancer patients. The CBR in this study was close to the data reported in Chinese and foreign literature, but the CBR of the first-line therapy (85.0%) was higher than that in the Chinese and foreign literature reports, which may be due to the smaller number of patients receiving first-line therapy [10-13].

Everolimus mainly produces adverse reactions such as stomatitis, rash, fatigue, diarrhea, interstitial pneumonia, infection and metabolic abnormalities. Among them, the most common ones are stomatitis, infection and malnutrition events [14], whereas severe adverse reactions include interstitial pneumonia, stomatitis, infection and renal failure. Most of them belong to grade II/III changes and can be mitigated through active symptomatic treatment. The perianal abscess observed in the present study has not been reported in previous Chinese and foreign studies, with its cause remaining unclear. In the present study, the incidence rate of adverse reactions observed was higher. In particular, the incidence rates of oral mucositis and interstitial pneumonia were higher than those in a study in China and beyond, which may be associated with the poor immunity and general conditions of patients at enrollment [15].

Based on the relevant literature reports in China and foreign countries, the mPFS was 4.0-8.6 months in the advanced breast cancer patients who were treated with everolimus combining endocrine drugs [12,13,16-18]. The results of this study showed that the mPFS of the two groups of patients was 7.3±5.6 and 6.7±5.1 months, respectively, which are close to the figures in the study reports in China and beyond.

The results of the BOLERO-2 trial suggested that compared with placebo combined with endocrine therapy, everolimus combined with endocrine therapy can significantly prolong the mPFS

of patients with visceral metastases (6.8 *vs.* 2.8 months, p<0.05) and those with no visceral metastases (9.9 *vs.* 4.2 months, p<0.05), and greatly extends the mPFS of patients by up to 4 months regardless of the presence or absence of visceral metastases [19]. In the present study, the mPFS of patients with no visceral metastases was longer than that of patients with visceral metastases by 4 months (11.1±4.2 months *vs.* 5.9±3.4 months), consistent with the results in the relevant literature reports. The above results indicate that the addition of everolimus can also enhance the sensitivity of visceral metastasis patients with no obvious symptoms to endocrine therapy, and that everolimus combined with endocrine therapy is probably a potential novel alternative to chemotherapy, but it remains to be further explored through clinical studies.

A study reported that the everolimus combined with endocrine therapy enables the mPFS to reach 3.0-5.4 months and 3.0-14.8 months, respectively, in patients with primary and secondary resistance [13]. According to the results of this study, the mPFS was 8.6±3.8 months in patients previously sensitive to endocrine therapy and 4.8±3.2 months in those previously insensitive to endocrine therapy, and everolimus combined with endocrine therapy was more beneficial for the patients previously sensitive to endocrine therapy, agreeing with the results in related literature reports.

The present study has some shortcomings, including limited sample number, relatively short follow-up time and less comprehensive follow-up contents, so the conclusion of this study needs the data support from the forthcoming prospective clinical studies featuring strict design, high reliability and large sample size.

Conclusions

Everolimus combined with endocrine therapy has significant clinical efficacy in patients with HR-positive/HER-2-negative advanced breast cancer, and can effectively improve the survival of patients, with tolerable tolerate adverse reactions. PR^+, absence of visceral metastases and sensitivity to endocrine therapy are the protective prognostic factors for PFS.

Conflict of interests

The authors declare no conflict of interests.

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