Original Article

Efficacy and safety of low-dose everolimus combined with endocrine drugs for patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer

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Background: To analyze the efficacy and safety of everolimus 5 mg/day in combination with endocrine drugs in the treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer using real-world clinical data.

Methods: Clinical data of hormone receptor (HR)-positive and HER2-negative patients with advanced breast cancer treated with everolimus combined with endocrine drugs in our center between August 2012 and May 2017 were retrospectively analyzed. Curative effect and adverse reactions were evaluated.

Results: A total of 110 patients were enrolled in this study, and 87.3% received salvage chemotherapy. The median number of salvage treatment lines was 5 (range: 1–19). The median follow-up duration was 12 months (range: 1–56.3 months), the overall response rate (ORR) was 6.4%, the clinical benefit rate (CBR) was 31.8%, the median progression-free survival (mPFS) was 4.0 months (95% CI: 2.9–5.1 months), and the median overall survival (OS) was 17 months (95% CI: 12.1–21.9 months). The mPFS for patients who received ≤2 treatment line was 11.8 months (95% CI: 4.3–19.3 months). Univariate and multivariate analyses suggested that absence of liver metastases, secondary endocrine resistance, and number of metastasis sites <3 were the main factors influencing the benefit of everolimus combined with endocrine therapy. The most common adverse events of grade 3 were: stomatitis (5.5%), non-infectious pneumonia (1.8%), and erythra (1.8%). No grade 4 adverse reactions were observed.

Conclusions: Our results showed that everolimus (5 mg/day) combined with endocrine therapy was effective and relatively safe for patients with hormone receptor-positive, HER2-negative metastatic breast cancer.

Keywords: Everolimus; hormone receptor-positive; metastatic breast cancer; endocrine therapy; real world

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Introduction

Breast cancer is the most common malignant tumor in women, with an increasing incidence worldwide (1). Approximately 70–80% of patients with breast cancer are diagnosed with hormone receptor (HR)-positive luminal A or luminal B subtype. Endocrine therapy is an important treatment approach for hormone receptor-positive patients; yet, some patients may develop primary and secondary resistance (2-4). Endocrine resistance seems to be associated with the activation of multiple growth factor signaling pathways. The interaction between estrogen receptors (ER) and the phosphatidylinositol 3-kinase/protein kinase B/mammalians target of rapamycin (PI3K/AKT/mTOR) signaling pathways can activate the ER pathway in a ligand-dependent and ligand-independent manner, which leads to further proliferation and development of tumors (5,6). Recent preclinical studies have revealed that PI3K/AKT/mTOR pathway inhibitors may reverse endocrine resistance (7,8).

Everolimus is an oral mTOR pathway inhibitor. Three prospective randomized studies, PrECOG0102 II, TAMRAD/GINECO, and BOLERO-2, along with the recent observational studies (STEPAUT, EVEREXES, 4EVER, and BRAWO), have demonstrated that everolimus combined with endocrine therapy can extend progression-free survival in patients who did not respond well to initial endocrine therapy (9-12). The initial dose of everolimus used in overseas clinical studies was 10 mg/day (13-15); however, in the BOLERO-2 and BALLET studies, the dose was reduced or the medication was discontinued due to the occurrence of adverse reactions in 62% and 59.6% of patients, respectively (16,17). Ciccarese *et al.* (18) retrospectively analyzed the efficacy and safety of everolimus administered at different initial doses (10 mg/day, 5 mg/day) in 163 patients and reported no significant differences in the effectiveness and progression-free survival (PFS) between the two groups, while the tolerance was worse in the high-dose group. Everolimus combined with endocrine therapy is likely safe and effective in older patients with HR-positive and HER2-negative metastatic breast cancer (19). There is no definite biomarker to predict the efficacy and safety of everolimus combined with endocrine drugs.

In China, there is still a lack of clinical data on everolimus. Gong *et al.* (20) showed that among the 54 patients who received an initial dose of everolimus of 10 mg/day, the dose was reduced to 5 mg/day in 11 cases (20%) due to adverse reactions. When we started administering everolimus, the initial dose of everolimus, which was 10 mg/day, was not well tolerated by a high number of patients, and thus it was reduced to 5 mg/day. In this study, we summarized real-world clinical data from our center to evaluate the effectiveness and safety of everolimus (5 mg/day) combined with endocrine therapy in the treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4273).

Methods

Study population

Clinical data of HR-positive and HER-2 negative patients with metastatic breast cancer who received everolimus combined with endocrine therapy in our center between August 2012 and May 2017 were selected. Inclusion criteria were: (I) aged ≥18 years; (II) patients histopathologically confirmed with unresectable advanced or metastatic disease breast cancer; (III) HR-positive was defined as the proportion of positive cells >1% using estrogen receptor (ER) or progestogen receptor (PR) immunohistochemistry (IHC), while HER2-negative was defined as IHC 0-1+ or fluorescence in situ hybridization (FISH)/chromogenic in situ hybridization (CISH)-negative; (IV) Eastern Cooperative Oncology Group (ECOG) score was 0–2 points; (V) patients who did not respond well to previous adjuvant endocrine therapy or salvage endocrine therapy, i.e., recurrence occurred during or after adjuvant endocrine therapy or progression during salvage endocrine therapy; (VI) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 standard, there was at least one extracranial measurable lesion or the patient had osteolytic or mixed bone metastases; (VII) normal blood routine tests and normal liver and kidney function. Exclusion criteria were: (I) pregnant or lactating; (II) life expectancy <3 months; (III) patients with uncontrolled lung diseases, severe infections, heart disease, and diabetes that required treatment, and coagulopathy to which the patients were intolerant; (IV) patients who previously suffered from other malignancies except for cervical cancer and non-melanoma skin cancer with a disease-free survival up to 5 years.

Complete medical data were collected, which included clear clinicopathological information, treatment records,

evaluation of follow-up records, etc. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The Fifth Medical Center of the Chinese People's Liberation Army General Hospital (formerly named the 307 Hospital of Chinese People's Liberation Army) (No. 2010-06-64) and informed consent was taken from all the patients.

Therapeutic methods

The initial dose of everolimus was 5 mg/day. If there were adverse reactions, the medication was adjusted to be permanently withdrawn or administration was delayed. Adverse events were treated according to guidelines. The endocrine drugs combined with everolimus were given based on previous clinical studies and at the discretion of the treating physicians. After excluding the endocrine drugs that have previously proven as ineffective, those administered during the present study included: selective estrogen receptor modulators (SERMs), including tamoxifen (20 mg/day, orally) and toremifin (60 mg/day, orally); aromatase inhibitors (AIs), including letrozole (2.5 mg/day, orally), anastrozole (1 mg/day, orally), exemestane (25 mg/day, orally), fulvestrant (500 mg 1/28 day, intramuscular injection), and medroxyprogesterone (1,000 mg/day, orally).

Efficacy evaluation criteria and observation indexes

Drug efficacy and adverse events were routinely recorded every 2 months. The discontinuation of medication was based on the disease's progression or the emergence of intolerable adverse reactions. Follow up lasted until November 2017. Drug effectiveness was evaluated based on the RECIST version 1.1 criteria (21). Adverse reactions were judged according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE 4.0). The observation indexes included PFS, overall survival (OS), clinical benefit rate (CBR), and objective response rate (ORR). Progression-free survival was defined as the time interval from the start of treatment to the first disease progression or death from any cause; CBR as the proportion of patients achieving a complete response (CR), partial response (PR), or stable disease (SD) for ≥6 months during the treatment period. Overall response rate (ORR) referred to the proportion of patients with CR and PR.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 software. Measurement data were expressed as medians (ranges); count data were expressed as adoption rates or composition ratios. Chi-square test or Fisher's exact test was used to analyze group differences. Kaplan-Meier curves and log-rank tests were used for analyzing PFS and OS. Cox regression models were used to calculate the hazard ratios (HR) and 95% confidence intervals (CIs). Log-rank tests were used for univariate analyses, including age, disease-free survival (DFS), number of metastatic organs (1–2 *vs.* ≥3), visceral metastases, liver/lung/bone metastases, previous salvage chemotherapy, number of lines of endocrine therapy, endocrine resistance (primary *vs.* secondary), and combined drugs for endocrine therapy. Primary endocrine resistance was defined as relapse within 2 years of auxiliary endocrine therapy or progression within 6 months of salvage endocrine therapy. Secondary endocrine resistance was defined as relapse after 2 years of auxiliary endocrine therapy or within 1 year after the end of auxiliary endocrine therapy or progression after 6 months of salvage endocrine therapy. Cox multivariate analyses were performed based on the results of univariate analyses. P values and CIs were both bilaterally tested. P value <0.05 was considered as indicating statistical significance.

Results

Patient characteristics and prior treatment

A total of 110 patients were enrolled in this study. General patient data are shown in *Table 1*. The median age was 50 years (range: 30–74 years), and 63.6% of patients were postmenopausal. Premenopausal patients received drug-induced ovarian function suppression and were treated in accordance with the criteria for postmenopausal patients. All patients had received endocrine therapy in the adjuvant or late stage, and 87.3% received salvage chemotherapy. Moreover, 69.1% of patients had visceral metastases, 72.7% had received ≥3 treatment lines previously, and only 2.7% received everolimus as first line treatment. The median number of salvage treatment lines, median number of salvage endocrine therapy lines, and median number of salvage chemotherapy lines were 5 [1–19], 3 [1–8], and 3 [0–11], respectively. Moreover, 56.1% of patients had received chemotherapy, and 43.9% of patients had received endocrine therapy recently.

Table 1 General characteristics

Characteristic	Number of cases (%)
Age (year)	
Median [range]	50 [30–74]
Body mass index (kg/m^2)	
Median [range]	24.1 [17.8–34.8]
Mean (SD)	24.3 (3.2)
Menopausal status	
Postmenopausal	70 (63.6)
Premenopausal	40 (36.4)
Disease-free survival (month)	
Median [range]	36 [0–276]
≤12	22 (20.0)
12–24	21 (19.1)
>24	67 (60.9)
Number of metastatic sites	
1	24 (21.8)
2	24 (21.8)
≥3	62 (56.4)
Metastasis site	
Bone	80 (72.7)
Viscera	76 (69.1)
Liver	51 (46.4)
Lung	48 (43.6)
Previous endocrine therapy	
Tamoxifen	77 (70.0)
Letrozole or anastrozole	86 (78.2)
Exemestane	58 (52.7)
Fulvestrant	37 (33.6)
Endocrine drugs during last therapy	
Tamoxifen	15 (13.6)
Letrozole or anastrozole	32 (29.1)
Exemestane	28 (25.5)
Fulvestrant	29 (26.4)
Combined endocrine drugs	
Anti-estrogens	19 (17.3)
Letrozole or anastrozole	25 (22.7)
Exemestane	45 (40.9)
Fulvestrant	20 (18.2)
Medroxyprogesterone	1 (0.9)
Number of lines of salvage endocrine therapy	
Median [range]	3 [1–8]
1	11 (10.0)
2	36 (32.7)
≥3	63 (57.3)
Number of lines of salvage chemotherapy	
Median [range]	3 [0–11]
0	14 (12.7)
1	20 (18.2)
2	17 (15.5)
≥3	59 (53.6)

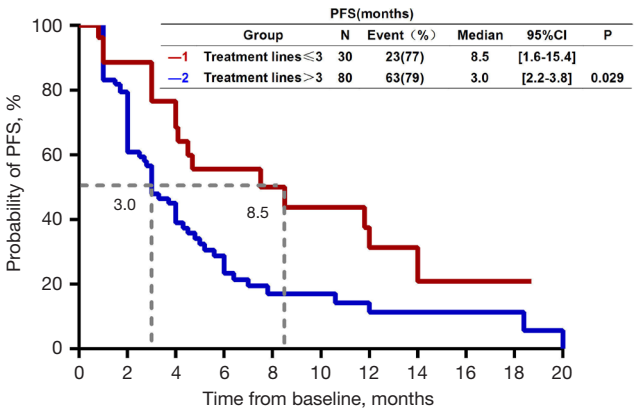

Figure 1 Progression-free survival curves for patients on different numbers of treatment lines.

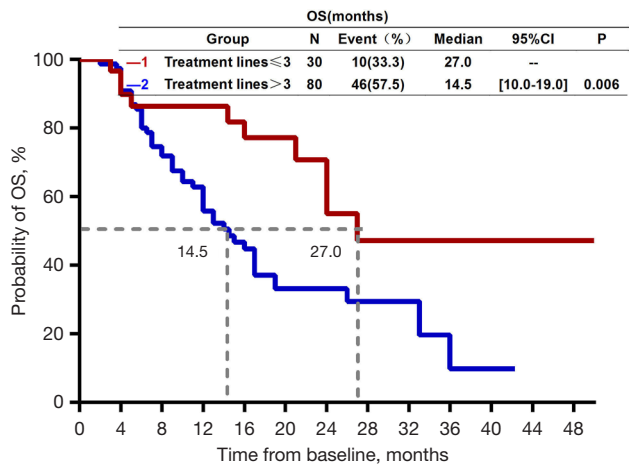

Figure 2 Overall survival curves for patients on graded number of treatment lines.

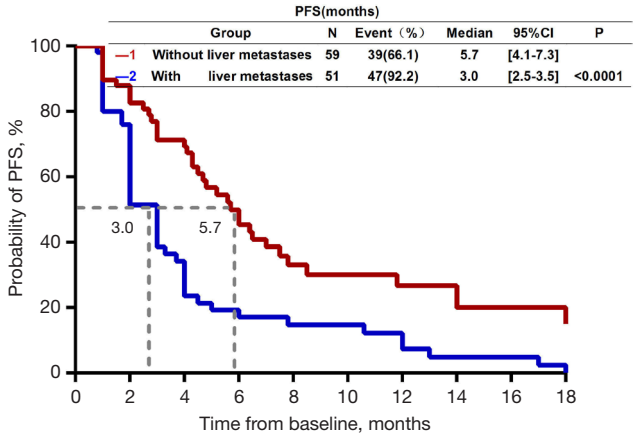

Figure 3 Progression-free survival curves for patients with or without liver metastases.

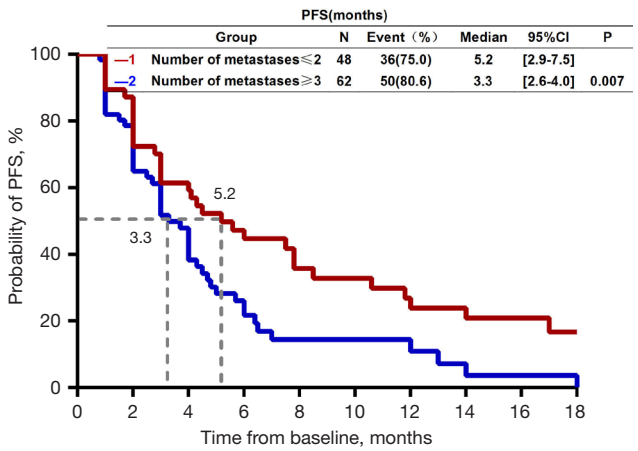

Figure 4 Progression-free survival curves for patients with different numbers of metastases.

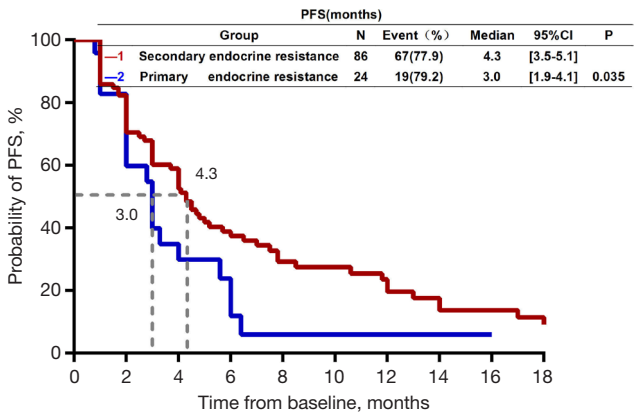

Figure 5 Progression-free survival curves for patients with primary and secondary endocrine resistance.

Efficacy

Until November 2017, the median follow-up period was 12 months (range: 1–56.3 months). Treatment was terminated in 86 patients (78.2%) due to disease progression; medication was discontinued in 12 patients (10.9%) due to intolerance of adverse reactions to everolimus and in 7 patients (6.4%) due to other reasons; and treatment was continued in 5 patients (4.5%). Fifty-six patients (50.9%) died, 13 patients (11.8%) were lost to follow-up, and 41 (37.3%) patients survived. Among the 110 patients, there were 7 cases of partial response, and 28 cases of stable disease exceeding 6 months, no complete response case. The ORR was 6.4%, the CBR was 31.8%, the median progression-free survival (mPFS) was 4.0 months (95% CI: 2.9–5.1 months), and the median OS was 17 months (95% CI: 12.1–21.9 months). The mPFS of patients who received ≤2 treatment lines was 11.8 months (95% CI: 4.3–19.3 months), and that of patients who received ≤3 treatment lines was 8.5 months (95% CI: 1.6–15.4 months). Compared with patients who received >3 treatment lines, the PFS and OS of patients who received ≤3 treatment lines were significantly longer (*Figures 1,2*). Among the 40 patients (36.4%) with resistance to non-steroidal aromatase inhibitors who received everolimus combined with exemestane, the mPFS of 11 patients (27.5%) who received ≤3 treatment lines was 8.5 months (95% CI: 1.0–16.4 months). Univariate and multivariate analyses showed that patients without hepatic metastases and secondary endocrine resistance and number of metastatic sites <3 were more likely to benefit from everolimus combined with endocrine therapy (*Figures 3-5*, *Tables 2,3*). Following the principle of avoiding the use of previously ineffective endocrine drugs, the combinations of everolimus with different endocrine drugs did not show significant differences (*Figure 6*).

Adverse reactions

The adverse events of the 110 patients are listed in *Table 4*. No grade 4 adverse reactions were observed, and no patients died of treatment-related adverse reactions. Administration of everolimus was discontinued in 12 patients (10.9%) due to adverse reactions, including 6 cases of non-infectious pneumonia, 1 case of stomatitis (grade 3 adverse reactions), 2 cases of non-inductive pneumonia and stomatitis, 1 case of erythra (grade 3 adverse reactions), 1 case of hemorrhagic cystitis, 1 case of proteinuria. The incidence of non-

Table 2 Univariate analysis of factors affecting PFS

Factor	PFS (month)	HR	95% CI	P
Age		0.92	0.54–1.6	0.767
<60, n=88	4.0			
≥60, n=22	4.1			
Body mass index		0.98	0.64–1.5	0.911
< Mean, n=60	3.0			
≥ Mean, n=47	4.5			
Combined endocrine drugs		1.0	0.81–1.25	0.367
Anti-estrogens, n=19	4.7			
Letrozole or anastrozole, n=25	4.3			
Exemestane, n=45	4.0			
Fulvestrant, n=20	3.0			
Medroxyprogesterone, n=1	1.7			
Liver metastases		2.1	1.36–3.24	<0.0001
No, n=59	5.7			
Yes, n=51	3.0			
Lung metastases		1.25	0.81–1.92	0.297
No, n=62	4.3			
Yes, n=48	4.0			
Bone metastases		1.81	1.09–2.99	0.015
No, n=30	6.0			
Yes, n=80	3.0			
Number of metastasis sites		1.79	1.15–2.80	0.007
≤2, n=48	5.2			
≥3, n=62	3.3			
Number of lines of salvage chemotherapy		1.74	1.13–2.69	0.008
≤2, n=51	5.2			
≥3, n=59	3.0			
Menstrual status		1.04	0.67–1.61	0.869
Premenopausal, n=40	4.0			
Postmenopausal, n=70	4.0			
Endocrine resistance		0.61	0.36–0.81	0.035
Primary resistance, n=24	3.0			
Secondary resistance, n=86	4.3			
Disease-free survival		0.85	0.55–1.31	0.438
≤24 months, n=43	3.0			
>24 months, n=67	4.0			
Grade of treatment line		1.67	1.03–2.7	0.029
≤3, n=30	8.5			
>3, n=80	3.0			
Grade of endocrine line		1.43	0.92–2.22	0.095
≤2, n=47	4.5			
≥3, n=63	3.3			

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

Table 3 Multivariate analysis of factors affecting PFS

Factor	PFS (month)	HR	95% CI	P
Liver metastases		2.04	1.31–3.18	0.002
No, n=59	5.7			
Yes, n=51	3.0			
Bone metastases		1.48	0.86–2.54	0.133
No, n=30	6.0			
Yes, n=80	3.0			
Number of metastasis sites		1.72	1.09–2.72	0.021
≤2, n=48	5.2			
≥3, n=62	3.3			
Number of lines of salvage chemotherapy		1.11	0.59–2.11	0.48
≤2, n=51	5.2			
≥3, n=59	3.0			
Endocrine resistance		0.52	0.30–0.88	0.015
Primary resistance, n=24	3.0			
Secondary resistance, n=86	4.3			
Grade of treatment line		1.02	0.52–2.01	0.765
≤3, n=30	8.5			
>3, n=80	3.0			

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

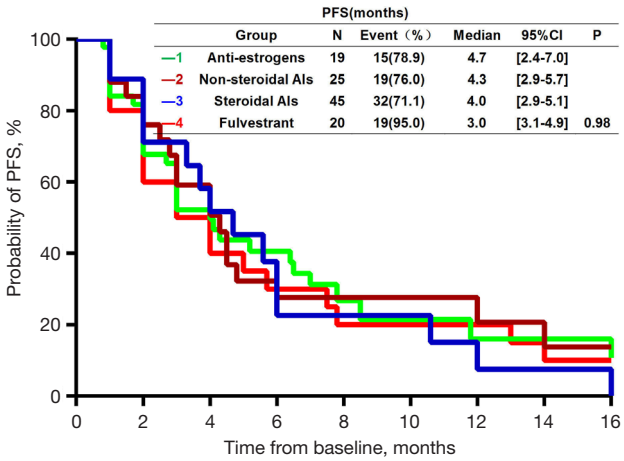

Figure 6 Progression-free survival curves for patients on different endocrine drugs.

Table 4 Adverse reactions

Adverse reactions	All grades (n, %)	≥ Grade 3 (n, %)
Non-hematological adverse reactions		
Stomatitis	24 (21.8)	6 (5.5)
Non-infectious pneumonia	22 (20.0)	2 (1.8)
Fatigue	20 (18.2)	0 (0)
Erythra	10 (9.1)	2 (1.8)
Body weight loss	7 (6.4)	0 (0)
Hematological adverse reactions		
Anemia	25 (22.7)	0 (0)
Leukopenia	15 (13.6)	1 (0.9)
Thrombocyopenia	14 (12.7)	1 (0.9)
Elevated blood sugar	26 (23.6)	1 (0.9)
Elevated alanine aminotransferase	31 (28.2)	0 (0)
Elevated aspartate aminotransferase	40 (36.4)	0 (0)

hematologic and hematological adverse reactions was lower or similar to that reported in previous studies.

Discussion

Resistance to endocrine therapy remains a big challenge in clinical practice. CDK4/6 inhibitors have significantly improved overall survival for patients with HR-positive and HER2-negative advanced breast cancer, while this study is the clinical application of everolimus before approval of CDK4/6 inhibitors in China. There have been clinical data indicated that everolimus maybe a potential treatment after CDK4/6 inhibitors resistance (22). One of the mechanisms of endocrine resistance is the activation of the growth factor receptor PI3k/AKT/mTOR signaling pathway. The BOLERO-2 study (23) compared the efficacy of a combination of the mTOR inhibitor everolimus with the endocrine therapy exemestane and exemestane alone in advanced breast cancer patients with resistance to endocrine therapy. The results revealed that the combination therapy could significantly prolong PFS. The BOLERO-2 study confirmed that everolimus combined with exemestane could effectively improve PFS in patients with advanced breast cancer who did not respond well to non-steroidal aromatase inhibitors. Everolimus combined with endocrine drugs might be considered a cost-effective option compared with other endocrine therapies for HR-positive and HER2-negative metastatic breast cancer as second-line therapy (24). However, in the BOLERO-2 study, patients showed a higher rate of treatment interruption and an increased incidence of adverse reactions. The median dose of everolimus was 8.6 mg/day, and the dose ranged from 0.9–1.1 and 0.5–0.7 in 19% and 17% of patients, respectively. Moreover, in 62% of patients the dose was reduced or interrupted (16). The subgroup analysis showed that the overall incidence of adverse reactions such as stomatitis, pneumonia, and erythra in Asians (excluding Chinese) was higher than in non-Asians, with a similar incidence of grade 3 or higher adverse reactions (23). In the BALLET study, medication was interrupted in 56.2% of patients who received everolimus 10 mg/day; the dose was changed in 59.6% of patients, which was similar to the results reported in BOLERO-2 (17). Xu *et al.* showed that in Chinese patients, the incidence of adverse reactions in the everolimus 10 mg group was almost twice that of the 5 mg group, and the absolute value of efficiency of the 5 mg group was higher than that of the 10 mg group (25). In the present study, everolimus treatment was discontinued in 12 patients due to adverse reactions, while in only 3 (2.7%) patients, it was discontinued due to grade 3 adverse reactions.

Ciccarese *et al.* (18) retrospectively analyzed the efficacy and safety of everolimus administered at different initial doses (10 mg/day, 5 mg/day) in 163 patients. These patients were divided into Groups A, B, and C according to different doses of everolimus. Group A, which included 84 patients (51.6%), was continuously given 10 mg/day or resumed a dose of 10 mg/day if there were temporary interruptions;

Group B, which included 54 patients (33.1%), was given an initial dose of 5 mg/day or an initial dose of 10 mg/day, which was subsequently reduced to 5 mg/day; and Group C consisted of 25 patients (15.3%) and was given 10 or 5 mg/day. The results revealed drug effectiveness of 29.8% and 27.8%, and PFSs of 9 and 10 months in Groups A and B, respectively, thus suggesting no significant difference between the 10 mg/day group and 5 mg/day group. In the present study, we retrospectively analyzed the real-world clinical data of advanced breast cancer patients with hormone receptor-positive, who were given everolimus (5 mg/day) combined with endocrine drugs. We found that in patients who received ≤2 and ≤3 treatment lines, had mPFSs of 11.8 and 8.5 months, respectively, which was comparable to the retrospective analysis results reported by Ciccarese *et al.* (18). Meanwhile, in the BOLERO-2 study, the mPFS of everolimus combined with exemestane was 11 months, which was similar to that of patients who received ≤2 treatment lines in the present study. The reason for the similar drug effectiveness may be due to the good tolerability of everolimus at a dose of 5 mg/day, which leads to better treatment compliance and similar drug effectiveness compared with a dose of 10 mg/day. Another study (26) showed that a low body mass index (BMI) might indicate better effectiveness of everolimus combined with exemestane, which suggests that an everolimus dose of 5 mg/day may be feasible in the Chinese population as their median BMI is lower than that of European and American patients.

This study has the following limitations: it is a single-center retrospective study with a relatively small sample size, which may lead to certain biases.

Conclusions

Everolimus (5 mg/day) combined with endocrine therapy is effective and relatively safe for patients with hormone receptor-positive metastatic breast cancer. The absence of liver metastases, secondary endocrine resistance, and a number of metastasis sites <3 were among many factors influencing the benefit of everolimus combined with endocrine therapy. Additional studies with larger sample sizes are required to confirm these findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-4273

Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-4273

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-4273). 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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The Fifth Medical Center of the Chinese People's Liberation Army General Hospital (formerly named the 307 Hospital of Chinese People's Liberation Army) (No. 2010-06-64) and informed consent was taken from all the patients.

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