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ORIGINAL ARTICLE

Efficacy of fulvestrant in treating postmenopausal patients with estrogen receptor-positive metastatic breast cancer and prognostic analysis

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Summary

Purpose: *To explore the efficacy and safety of 500 mg of fulvestrant for the postmenopausal patients with estrogen receptor (ER)-positive metastatic breast cancer, and to analyze the factors affecting the prognosis of patients.*

Methods: *A retrospective analysis was conducted on the clinical data of 86 postmenopausal patients with ER-positive metastatic breast cancer, who were admitted to our hospital from January 2015 to December 2016, and these patients were treated with 500 mg of fulvestrant. The clinical efficacy and incidence of adverse reactions were evaluated. Moreover, the patients were followed up for recording the survival and disease progression. Finally, survival analysis was carried out using the Kaplan-Meier method, log-rank test and Cox's proportional hazards regression model.*

Results: *Among the 86 patients, 7 achieved partial response (PR), with an objective response rate (ORR) of 8.1%, and 44 (51.2%) had stable disease (SD), including 21 cases of SD ≥24 weeks, and the clinical benefit rate (CBR) [proportion of cases of complete response (CR) + PR +SD ≥24 weeks] was 36.0% (31/86). The remaining 35 (40.7%) patients suffered from progressive disease (PD) according to the initial efficacy assessment at 2-3 months after treatment. According to the follow-up results, the median overall survival (mOS) and median progression-free survival (mPFS) of patients were 26.7±6.9 months and 6.5±4.1 months, respectively. The 1-year and 2-year OS rates were 60.5% and 33.7%, respectively showing that the risk of PD in patients with visceral metastasis and taking tamoxifen was 2.443 times higher vs those not taking tamoxifen (p=0.031 vs (p=0.024). Besides, the mPFS was significantly prolonged in patients undergoing no endocrine therapy previously, and patients receiving first-line therapy of fulvestrant in this study [hazard ratio (HR) =1.942, 95% CI: 0.774-2.483, p=0.037, HR=0.863, 95% CI: 0.688-0.981, p=0.013).*

Conclusion: *Fulvestrant has definite efficacy in treating ER-positive metastatic breast cancer and results in tolerable adverse reactions, while it notably extends the mPFS of patients who have no visceral metastasis and receive no prior tamoxifen or endocrine therapy, but the first-line fulvestrant therapy in this study.*

Key words: *fulvestrant, estrogen receptor-positive, postmenopausal, breast cancer, metastasis, efficacy, prognosis*

Introduction

Hormone receptor-positive breast cancer is an important molecular subtype of breast cancer, whose prognosis is closely associated with the expression of hormone receptors and the selection of endocrine therapy [1]. Endocrine therapy is the preferred treatment for estrogen receptor (ER)-positive metastatic breast cancer [2]. Among drugs such as aromatase inhibitors, novel ERs and ER down-regulators, aromatase inhibitors are currently the first choice for most postmenopausal patients with ER-positive breast cancer, but many of them are likely to suffer from cross resistance and rapid relapse [3, 4].

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Fulvestrant is a novel ER antagonist and down-regulator that can bind to ERs and block and down-regulate them under high affinity, thereby inactivating the transcription activation function 1 (AF1) and AF2 in ERs and accelerating the loss of ERs [5,6]. Compared with tamoxifen that only blocks AF2, fulvestrant exerts a complete anti-ER effect, without activating ERs, so it is mainly applied to the rescue treatment of metastatic breast cancer after the failure of previous endocrine therapy [7]. Fulvestrant at a dose of 250 mg and 500 mg was approved for marketing in 2011 and 2015, respectively, in China. According to the indications in foreign countries and recommendations in the guidelines in China and abroad, 500 mg of fulvestrant has been extensively applied clinically [8,9]. In this study, the efficacy and safety of 500 mg of fulvestrant for postmenopausal patients with ER-positive metastatic breast cancer were retrospectively analyzed, so as to provide a basis for developing clinical strategies to treat such patients.

Methods

General data

Clinical data were collected from 86 postmenopausal patients with ER-positive metastatic breast cancer, who were treated with 500 mg of fulvestrant in our hospital from January 2015 to December 2016. Inclusion criteria: 1) patients with primary tumor that was confirmed pathologically as breast cancer, 2) those with metastases proved by CT, MRI, ECT and other imaging examinations or pathology, 3) those whose ER/PR status was re-determined by biopsy of metastases at more than 2 years after definite diagnosis, 4) those with measurable or evaluable lesions, 5) those with an Eastern Cooperative Oncology Group (ECOG) score of 0-1 point, and 6) those with expected survival ≥3 months. Exclusion criteria: 1) patients with severe dysfunctions of the liver, kidney or other solid organs, 2) those complicated with endocrine system-related diseases, such as hyperthyroidism or diabetes, 3) those with abnormal electrocardiograms and blood routine test results, or 4) those previously receiving fulvestrant therapy. All the enrollees were informed of this study and signed the informed consent in accordance with the *Declaration of Helsinki*. This study was approved by the ethics committee of Taizhou People's Hospital.

The 86 patients were 32-81 years old (median 56.67). Among them, there were 58 cases of natural menopause and 28 cases of inhibition of ovarian function by drugs or surgeries. Besides, 72.1% (62/86) patients underwent radical surgery for breast cancer, and 80.2% (69/86) had invasive ductal carcinoma. Lung, liver, bone and brain metastases occurred in 40.7% (35/86) cases, 27.9% (24/86) cases, 53.5% (46/86) cases and 4.7% (4/86) cases, respectively, and 24.4% (21/86) patients had only bone metastasis. Regarding the use of drugs, 57.0% (49/86) took tamoxifen, 60.5% (52/86) patients used letrozole, 25.6% (22/86) patients were given exemestane, and 41.9% (36/86) took anastrozole. Fulvestrant was used as first-line, second-line, third-line and above endocrine therapy in 30.2% (26/86), 33.7% (29/86) and 36.0% (31/86), respectively. The baseline data of patients are shown in Table 1.

Treatment methods

Fulvestrant was intramuscularly injected at 500 mg on d 1, d 14 and d 28. Then the administration was repeated every 28 d and lasted for 2 cycles at least, with 28 d as a cycle. The treatment ended when patients had progressive disease (PD) and intolerable adverse reactions, and they refused to be followed up or were lost to follow-up. The incidence of adverse reactions was assessed every 2-3 cycles.

Observation indicators

The therapeutic effect was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 [10] as follows: complete response (CR):

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

Characteristics	*Cases (n=86) n (%)*
Age (years), **mean±SD**	56.67±9.29
Pathological type	
Invasive ductal carcinoma	69 (80.2)
Invasive lobular carcinoma	7 (8.1)
Invasive poorly differentiated adenocarcinoma	10 (11.6)
Menstrual status	
Natural menopause	58 (67.4)
Drug-induced menopause	15 (17.4)
Surgery-induced menopause	13 (15.1)
Number of metastatic lesions	
1	37 (43.0)
2	31 (36.0)
≥3	18 (20.9)
Visceral metastasis	
Yes	48 (55.8)
No	38 (44.2)
Radical surgery	
Yes	62 (72.1)
No	24 (27.9)
Fulvestrant treatment	
First-line	26 (30.2)
Second-line	29 (33.7)
Third-line or more	31 (36.0)
ECOG PS	
0	19 (22.1)
1	67 (77.9)

ECOG: Eastern Cooperative Oncology Group

the disappearance of all lesions and no one or more new lesions, partial response (PR): a ≥30% decrease in the sum of the longest diameters of lesions, stable disease (SD): neither sufficient shrinkage of lesions to qualify for PR nor sufficient increase in lesions to qualify for PD, and PD: a ≥20% increase in the sum of the longest diameters of lesions or appearance of one or more new lesions. Objective response rate (ORR) was the ratio of the number of cases of CR + PR to the total case number, and clinical benefit rate (CBR) was the ratio of the number of cases of CR + PR + SD for ≥24 weeks to the total case number.

Clinical adverse events were graded based on the National Cancer Institute common toxicity criteria (NCI-CTC) version 4.03.

Patients were followed up at 1, 2, 3, 6, 9 and 12 months after treatment and then every 3-6 months until December 2019. Meanwhile, the survival and disease progression of patients were recorded. Progression-free survival (PFS) referred to the duration from the initiation of fulvestrant to the progression of tumors or death of patients. Overall survival (OS) was defined as the duration from the initiation of fulvestrant to the death of patients or the last follow-up.

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 performed using two-sample t-test. Enumeration data were presented as percentage (%), and x^2 test was performed for intergroup comparisons. The survival curves were plotted using the Kaplan-Meier method and log-rank test was used to compare survival between two groups. Univariate comparison between two groups was analyzed using the log-rank test. Multivariate analysis was carried out on the possible factors affecting the PFS of patients in the log-rank test using Cox's proportional hazards regression model. P<0.05 suggested statistically significant differences.

Results

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

A total of 86 patients with advanced breast cancer were treated with fulvestrant at a dose of 500 mg for more than 2 cycles, and their short-term outcomes were evaluable. The median treatment cycles were 5 (2-15 cycles). After all cycles of treatment, the efficacy was evaluated. Among the 86 patients, 7 achieved PR, with an ORR of 8.1%, and 44 (51.2%) had SD, including 21 cases of SD ≥24 weeks, and the CBR (proportion of cases of CR + PR + SD ≥24 weeks) was 36.0% (31/86). Besides, the remaining 35 (40.7%) patients suffered from PD according to the initial efficacy assessment at 2-3 months after treatment.

Table 2. Comparison of adverse reactions of the studied patients

Adverse reactions	*Cases*	
	Grade I-II *n (%)*	*Grade III-IV* *n (%)*
Fatigue	36 (41.9)	0 (0)
Hot flash	25 (29.1)	0 (0)
Loss of appetite	14 (16.3)	0 (0)
Nausea / Vomiting	16 (18.6)	0 (0)
Diarrhea	7 (8.1)	0 (0)
Arthralgia	9 (10.5)	0 (0)
Upper limbs numbness	8 (9.3)	0 (0)
Liver function damage	7 (8.1)	0 (0)
Injection site pain	19 (22.1)	0 (0)

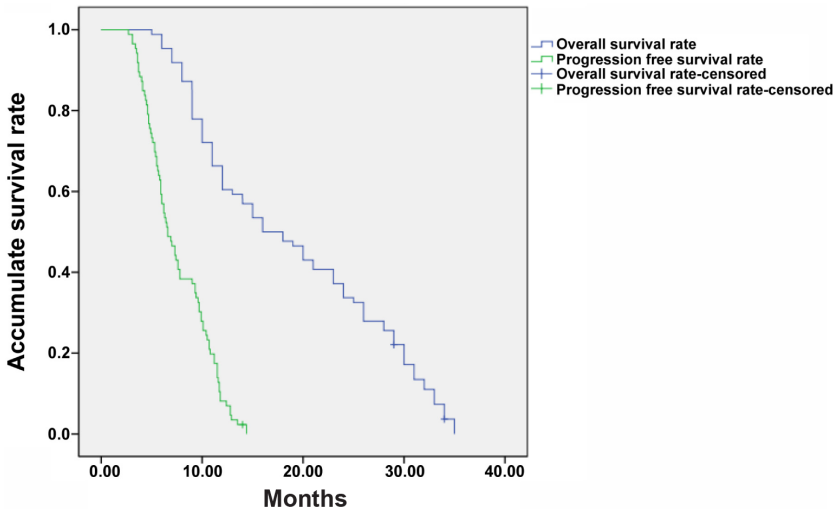

Figure 1. Kaplan-Meier survival curves of metastatic breast cancer patients showing overall survival rate and progression free survival rate of metastatic breast cancer (p<0.05).

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

The patients tolerated fulvestrant treatment well and had mainly the following treatment-related adverse reactions: fatigue, hot flash, loss of appetite, nausea and vomiting, diarrhea, arthralgia, upper limbs numbness, liver function damage and injection site pain, most of which were of grade I-II and resolved after symptomatic treatment. Fatigue, hot flash, nausea and vomiting, arthralgia and injection site pain had higher incidence rates and occurred in 36 cases (41.9%), 25 cases (29.1%), 16 cases (18.6%), 9 cases (10.5%) and 27 cases (31.4%), respectively. Moreover, 8 patients suffered from grade III-IV injection site pain. No severe adverse reactions were observed, and there were no deaths due to adverse reactions to the drug (Table 2).

Patient survival based on follow-up results

As of December 2019, the median follow-up time, median OS (mOS) and median PFS (mPFS) of 86 patients was 17.1±5.8, 26.7±6.9 and 6.5±4.1 months, respectively. Moreover, the 1-year and 2-year OS rates were 60.5% (52/86) and 33.7% (29/86), respectively (Figure 1).

Analysis of factors affecting the mPFS of patients

Univariate analysis was performed on the effects of age, menstrual status, number of cancer metastases, presence or absence of visceral me-

Table 3. Univariate analysis of predictors for mPFS in metastatic breast cancer patients

Parameters	*Cases (n=86)* *n (%)*	*mPFS (months)* *mean*±**SD**	*p value*
Age, years			0.066
<60	53 (61.6)	5.9±2.3	
≥60	33 (38.4)	7.1±3.2	
Menstrual status			0.133
Natural menopause	58 (67.4)	6.2±2.6	
Drug-induced menopause	15 (17.4)	5.9±2.2	
Surgery-induced menopause	13 (15.1)	7.7±3.0	
Number of metastasis lesions			0.113
1	37 (43.0)	6.6±2.8	
2	31 (36.0)	5.9±2.1	
≥3	18 (20.9)	5.1±2.5	
Visceral metastasis			0.034
Yes	48 (55.8)	6.0±2.6	
No	38 (44.2)	7.3±2.9	
Only bone metastasis			0.220
Yes	21 (24.4)	6.8±2.7	
No	65 (75.6)	6.1±2.1	
Radical surgery			0.183
Yes	62 (72.1)	6.6±2.9	
No	24 (27.9)	8.2±3.3	
Endocrine therapy timing			0.007
After metastasis	45 (52.3)	4.9±2.4	
Adjuvant therapy	32 (37.2)	7.1±3.9	
Not use	9 (10.5)	9.4±3.8	
Previous Tamoxifen treatment			0.001
Yes	49 (57.0)	4.7±2.2	
No	37 (43.0)	10.8±4.4	
Fulvestrant treatment			0.001
First-line	26 (30.2)	16.8±8.9	
Second-line	29 (33.7)	7.2±4.7	
Third-line or more	31 (36.0)	4.6±3.8	

mPFS: mean progression free survival

Table 4. Multivariate Cox regression analysis of predictors for mPFS in metastatic breast cancer patients

Parameters	*HR*	95%CI	*p value*
Visceral metastasis	2.443	1.768-4.567	0.031
Endocrine therapy timing	1.942	0.774-2.483	0.037
Previous Tamoxifen treatment	2.906	1.828-3.273	0.024
Fulvestrant as first-line treatment	0.863	0.688-0.981	0.013

HR: Hazard ratio; CI: Confidence interval

tastasis, only bone metastasis and prior radical surgery, previous timing for endocrine therapy, presence or absence of previous tamoxifen administration, and the number of lines of fulvestrant treatment on the mPFS of patients. According to the results, the mPFS in patients with visceral metastasis was significantly shorter than that in patients without visceral metastasis (6.0±2.6 months *vs.* 7.3±2.9 months, p=0.034). The patients previously undergoing no endocrine therapy after tumor metastasis had substantially longer mPFS than those previously receiving endocrine therapy after tumor metastasis or adjuvant endocrine therapy (9.4±3.8 months *vs.* 7.1±3.9 months or 4.9±2.4 months, p=0.007). Moreover, mPFS was significantly prolonged in patients who had not used tamoxifen compared with that in patients who had used tamoxifen (10.8±4.4 months *vs.* 4.7±2.2 months, p<0.001) and it was dramatically extended in patients administered fulvestrant as the first-line treatment compared with that in patients receiving second- and third-line fulvestrant treatment (16.8±8.9 months *vs.* 7.2±4.7 months and 4.6±3.8 months, p<0.001). The mPFS of patients was not correlated with the age, menstrual status, number of cancer metastases, presence or absence of only bone metastasis and presence or absence of prior radical surgery (Table 3).

The Cox proportional hazards regression analysis results showed that the presence or absence of previous tamoxifen use, presence or absence of visceral metastasis, previous timing for endocrine therapy, and the number of lines of fulvestrant treatment were independent risk factors for the mPFS of patients treated with fulvestrant. The risk of PD in patients with visceral metastasis and those previously taking tamoxifen was 2.443 times that in patients without visceral metastasis [95% confidence interval (CI): 1.768-4.567, p=0.031] and 2.906 times that in patients not taking tamoxifen (95% CI: 1.828-3.273, p=0.024), respectively. Besides, the mPFS was significantly prolonged in patients undergoing no endocrine therapy previously, and patients receiving first-line therapy with fulvestrant in this study [hazard ratio (HR) =1.942, 95% CI: 0.774-2.483, p=0.037, HR=0.863, 95% CI: 0.688-0.981, p=0.013) (Table 4).

Discussion

Endocrine therapy can benefit patients with hormone receptor-positive breast cancer. However, about 30% of them have resistance to primary endocrine therapy, and the vast majority of patients experience secondary resistance to the treatment with aromatase inhibitors as well after efficacious initial treatment. ER down-regulators are preferable options against the drug resistance [11]. Fulvestrant, a representative of ER down-regulators, has advantages such as a high response rate, a long validity period and mild adverse reactions [12]. According to the results of the international randomized, double-blind, parallel-controlled, multicenter, phase III CONFIRM study in 2014, fulvestrant is obviously dose-dependent. Specifically, the patients in 500 mg group had significantly longer PFS than those in 250 mg group (6.5 *vs.* 5.5 months, HR=0.8, 95% CI: 0.68-0.94, p=0.006), and the mOS was 26.4 months in the former and 22.3 months in the latter (HR=0.81, 95% CI: 0.69-0.96, p=0.02). The risk of PD was decreased by nearly 20% in the 500 mg group. The median duration of response was 16.6 months in 500 mg group and 13.9 months in 250 mg group, with no obvious difference between the two groups in terms of safety. The CONFIRM study confirmed that compared with 250 mg of fulvestrant, 500 mg of fulvestrant can reduce the risk of death by 19% and increase the mOS by 4.1 months, and it has better overall efficacy, with good tolerability for postmenopausal patients with hormone receptor-positive advanced breast cancer, who experience PD in the first-line endocrine therapy [13]. The succeeding CHINA CONFIRM study conducted by Chinese reseachers also confirmed that 500 mg of fulvestrant is more efficacious than 250 mg [14]. Therefore, 500 mg is routinely recommended as the dose of fulvestrant in the clinic.

The results of the international, randomized, double-blind, phase III clinical FALCON study revealed that the mPFS was 16.6 months (95% CI:

13.83-20. 99) and 13.8 months (95% CI: 11.99-16.59) in the fulvestrant group and anastrozole group, respectively, and the PFS was significantly extended in the former (HR=0.797, 95% CI: 0.637-0. 999, p=-0.0486) [15]. These results suggest that 500 mg of fulvestrant can be administered as the first-line endocrine treatment regimen for postmenopausal patients with ER-positive advanced breast cancer with no previous history of endocrine treatment. In another JBCRG-C06 Safari study for retrospectively analyzing the factors affecting the time to treatment failure (TTF) in advanced breast cancer patients treated with fulvestrant, 500 mg of fulvestrant were used as first-line therapy in 2.0% cases, as second-line therapy in 22.7% cases, as third-line therapy in 26.7% cases and as fourth-line and later-line therapies in 48.6%, and the median TTF was 5.4 months. Moreover, the multivariate analysis results suggested that the earlier-line treatment with fulvestrant at 500 mg (the first-line and second-line therapies *vs.* the third-line therapy *vs.* the fourth-line and later-line therapies, HR=-0.80, 95% CI: 0.74-0.86, p<0.001), longer time from definite diagnosis to initiation of fulvestrant (≥3 years *vs.* <3 years, HR=0.60, 95% CI: 0.51-0.70, p<0.001) and no prior palliative chemotherapy in patients with advanced or metastatic breast cancer (yes *vs.* no, HR=0.69, 95% CI: 0.60-0.80, p<0.001) were associated with obviously extended TTF [16], namely the earlier-line treatment with 500 mg of fulvestrant, no prior palliative chemotherapy and longer interval from definite diagnosis to initiation of fulvestrant correspond to a longer TTF.

In the present study, the patients treated with 500 mg of fulvestrant exhibited an ORR of 8.1%, CBR of 36.0%, mOS of (26.7±6.9) months and mPFS of (6.5±4.1) months. These results were basically consistent with previous literature reports, but the ORR and CBR were lower than those reported in the literature [13,17,18], probably because the patients enrolled in this study received later-line endocrine therapy. With regard to safety, the overall tolerance of patients in the present study was favorable, and the adverse reactions were mostly of grade I-II, without affecting normal treatment.

The factors affecting PFS were also analyzed in the present study, and the results of Cox proportional hazards regression analysis implied that the mPFS was considerably extended in patients without visceral metastasis, those not taking tamoxifen previously, those undergoing no endocrine therapy previously and those undergoing first-line fulvestrant therapy. As shown in the subgroup analysis of the SWOG-S0226 study, in the anastrozole and fulvestrant combination treatment group, the patients who had previously been given tamoxifen as adjuvant therapy had shorter PFS than those who had never used it (13.5 *vs.* 17.0 months), suggesting that patients not using tamoxifen can greatly benefit from fulvestrant [19]. The conclusion of the present study agrees with previous reports.

The present study has some shortcomings, including limited sample size, not comprehensive enough follow-up content, and enrollment of most metastatic breast cancer patients after prior first-line and second-line chemotherapy or radical surgery. Therefore, the conclusion of this study needs to be corroborated by the data from the rigorous, highly reliable, large-sample, multi-center prospective clinical studies in the future.

Conclusions

Fulvestrant has definite efficacy in treating ER-positive metastatic breast cancer and results in tolerable adverse reactions, and it notably extends the mPFS of patients who have no visceral metastasis and receive no prior tamoxifen or endocrine therapy, but the first-line fulvestrant therapy.

Conflict of interests

The authors declare no conflict of interests.

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