Real-World Efficacy of Fulvestrant Monotherapy as the First Treatment or Maintenance Treatment in Patients with Metastatic Breast Cancer

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Keywords

Metastatic breast cancer · Fulvestrant monotherapy · Real world · Maintenance treatment · First-line treatment

Abstract

Background: Fulvestrant 500 mg monotherapy is recommended as the first-line endocrine treatment in postmenopausal women with hormone receptor-positive metastatic breast cancer (MBC). It is also used in MBC maintenance treatment. However, few studies have compared the efficacy of fulvestrant during the initial treatment with that during maintenance treatment. **Patients and Methods:** MBC patients who were treated with fulvestrant either as initial therapy for metastatic disease or after progression following one line of chemotherapy between January 2016 and December 2017 were identified from the database of the Affiliated Hospital of Qingdao University. The primary end point was progression-free survival (PFS). **Results:** The study included 135 MBC patients who were treated with fulvestrant; 116 patients who received fulvestrant as first-line treatment were divided into 2 groups: the no-chemotherapy treatment (NCT) group received fulvestrant as initial therapy during disease progression, and the chemotherapy treatment (CT) group received fulvestrant as maintenance following disease stabilization or response to previous chemotherapy. The median PFS was 16 months in NCT patients and 8 months in the CT group. Patients who had a longer disease-free survival, no visceral metastasis and one metastasis site, benefited from fulvestrant as first-line treatment during disease progression. Patients with 2 or more metastasis sites bene-

fited from chemotherapy as first-line treatment and fulvestrant as maintenance treatment. **Conclusions:** Fulvestrant monotherapy showed good clinical activity and safety in patients with MBC who were treated upon disease progression and in those receiving maintenance therapy.

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Introduction

Breast cancer is a common malignant tumor in women worldwide. The incidence of breast cancer in the United States accounts for 30% of the total cancer incidence, and the mortality rate is approximately 15% according to the American Cancer Society. In China, the incidence and mortality of breast cancer in women are 15 and 6%, respectively [1, 2]. Hormone receptor (HR)-positive breast cancer accounts for 70–80% of all breast cancers. Approximately 40% of women who present with early-stage HR-positive breast cancer eventually develop metastatic disease [3]. Among these metastatic patients, endocrine therapy (ET) is the first choice of treatment as either the first line or second line even if patients have visceral metastasis (but not in cases of visceral crisis or ET resistance) [4]. The choice of endocrine drug depends on the previous treatment regimen and disease-free survival (DFS), and includes tamoxifen, aromatase inhibitors (AIs), or fulvestrant. However, some patients who are initially sensitive to ET develop resistance to ET [5]. Hence, the strategy and sequence of ET drugs are important.

Table 1. Clinical characteristics of ER-positive patients with fulvestrant usage ($n = 135$)

Covariate level	All patients ($n = 135$)	Fulvestrant usage		<i>p</i> value
		first line ($n = 116$)	≥second line ($n = 19$)	
Age at diagnosis, years	53 (27–82)	53 (27–82)	52 (30–71)	0.792
Age at fulvestrant usage, median years	57 (30–67)	57 (30–67)	55 (35–52)	0.620
ER, n (%)				
Negative	14 (10.37)	12 (10.34)	2 (10.5)	0.977
Positive	121 (89.63)	104 (89.65)	17 (89.5)	
PR, n (%)				
Negative	27 (20.00)	22 (18.97)	5 (26.32)	0.438
Positive	108 (80.00)	94 (81.03)	14 (73.68)	
HER2, n (%)				
Negative	108 (80.00)	91 (78.44)	17 (86.47)	0.538
Positive	14 (10.37)	13 (11.20)	1 (5.26)	
Unknown	13 (9.63)	12 (9.48)	1 (5.26)	
Histological grade, n (%)				
I	15 (11.11)	12 (10.34)	3 (15.79)	0.080
II	68 (50.37)	56 (48.28)	12 (63.16)	
III	52 (38.52)	48 (41.38)	4 (21.05)	
Stage, n (%)				
I	21 (15.55)	20 (17.44)	1 (5.26)	0.205
II	49 (36.30)	39 (33.85)	10 (52.63)	
III	53 (39.26)	45 (38.79)	8 (42.11)	
IV	12 (8.89)	12 (10.34)	0 (0)	
Metastatic sites, n (%)				
Lymph nodes	43 (31.85)	40 (34.88)	3 (15.79)	0.364
Bone	80 (59.26)	68 (58.62)	12 (63.12)	
Visceral	69 (51.11)	62 (53.44)	7 (36.84)	

Fulvestrant, a selective estrogen receptor (ER) degrader, binds to the ER, downregulating its expression and blocking ER function. It binds with 100-fold greater affinity than tamoxifen, and it is more effective than tamoxifen and AIs in inhibiting estrogen signaling [6, 7]. The CONFIRM trial, a phase 3 double-blind trial, divided patients with metastatic breast cancer (MBC) that progressed after previous endocrine treatment with tamoxifen or AIs into 2 groups: those receiving fulvestrant 500 mg and those receiving 250 mg [8]. The study showed that fulvestrant at 500 mg significantly improved progression-free survival (PFS) and the overall response rate compared with fulvestrant 250 mg. Hence, in subsequent clinical trials or in the clinic, fulvestrant 500 mg is the first choice compared with fulvestrant 250 mg. The First trial, a phase 2, double-blind clinical trial, randomized women who had not been previously treated into 2 groups treated with fulvestrant 500 mg or anastrozole [9]. The fulvestrant 500 mg group showed significantly improved PFS and overall survival compared with the anastrozole group. These results were confirmed in the phase 3 FALCON trial. The median PFS was 16.6 months in the fulvestrant 500 mg group and 13.8 months in the anastrozole group [10]. The American Society of Clinical Oncology therefore recommends fulvestrant 500

mg as the first-line treatment in postmenopausal women with HR-positive MBC.

However, breast cancer patients in clinical trials and in real world practice are different. For example, patients in the First and FALCON trials did not receive chemotherapy. In clinical practice, some patients receive chemotherapy before fulvestrant after progression. There are few data on the efficacy and safety of fulvestrant treatment in real-world practice, and whether fulvestrant is more effective as first-line or maintenance therapy remains unclear. In this study, we collected real-world data to retrospectively analyze the patterns of treatment and efficacy of fulvestrant in MBC patients, and we analyzed the factors affecting the response to treatment in HR-positive MBC patients.

Materials and Methods

Study Population

MBC patients who were treated with fulvestrant between January 2016 and December 2017 were included for study from the database of the Affiliated Hospital of Qingdao University. All tumors were ER and/or progesterone receptor (PR) positive (defined as ER or PR >1%) as determined by immunohistochemistry. All patients received fulvestrant 500 mg every 28 days after progres-

sion. Clinical data collected included age, ER/PR/HER2 status, histological grade, TNM stage, metastatic sites, and prior endocrine and cytotoxic chemotherapies.

Treatment Plan

HR-positive MBC patients received fulvestrant 500 mg until progressive disease, unacceptable toxicity, or loss of follow-up according to the approved national guidelines. Efficacy was determined according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.

Statistical Analysis

The primary end point of this study was PFS, defined as the time from initiation of post fulvestrant treatment to disease progression. The secondary aim of this study was the evaluation of adverse events, which were determined retrospectively based on medical records, including leukopenia, thrombocytopenia, anemia, hand-foot syndrome, atrial fibrillation, increased alanine aminotransferase levels, oral mucositis, myalgia, and nausea. The Kaplan-Meier and log-rank methods were used to analyze PFS curves. Differences were assessed using the χ^2 and Kruskal-Wallis tests. The risk factors and adjusted hazard ratios with 95% confidence intervals were calculated using the multivariable Cox proportional hazards model. All statistical analyses were performed using SPSS (version 23.0). Data were considered significant at $p < 0.05$.

Results

Patients and Treatment

In total, 135 patients with MBC from the Affiliated Hospital of Qingdao University breast cancer database treated with fulvestrant 500 mg between January 2016 and December 2017 were analyzed. The clinical features of these patients are presented in Table 1.

The study included 135 patients, of which 116 (85.9%) received fulvestrant as first-line ET and 19 (14.1%) received fulvestrant as the second line or later lines of ET. There were no significant differences in clinical features such as age, tumor grade, ER/PR/HER2 expression levels, stage, and metastatic sites (Table 1). However, our study indicated that patients with later stage and worse grade would prefer to receive fulvestrant as the second line.

Nineteen patients received other endocrine treatments before fulvestrant including NSAIDs (nonsteroidal anti-inflammatory drugs), exemestane, or exemestane + everolimus. To identify the factors affecting the efficacy of first-line fulvestrant treatment, we divided the 116 patients who received fulvestrant as the first-line ET into 2 groups, a no-chemotherapy treatment (NCT) group and a chemotherapy treatment (CT) group before fulvestrant treatment during disease progression. The most frequently ($\geq 10\%$) used chemotherapy regimens were docetaxel-based in 42.5%, capecitabine in 27.5%, and carboplatin-based in 20% of patients.

Of these patients, 76 (65.5%) did not receive chemotherapy before fulvestrant, whereas 40 (34.5%) were treat-

Table 2. Clinical characteristics of NCT and CT group patients

Characteristics	NCT, % (76; 65.5%)	CT, % (40; 34.5%)	<i>p</i> value
Median age, years	58	54	0.604
DFI, <i>n</i> (%)			0.603
≤24 months	23 (30.3)	14 (35.0)	
>24 months	53 (69.7)	26 (65.0)	
ER, <i>n</i> (%)			0.701
Negative	6 (7.9)	4 (10.0)	
Positive	70 (92.1)	36 (90.0)	
PR, <i>n</i> (%)			0.344
Negative	17 (22.4)	6 (15.0)	
Positive	59 (77.6)	34 (85.0)	
HER2, <i>n</i> (%)			0.112
Negative	62 (81.6)	31 (77.5)	
Positive	5 (6.58)	7 (17.5)	
Unknown	9 (11.8)	2 (5.0)	
Histological grade, <i>n</i> (%)			0.359
I	4 (5.3)	3 (7.5)	
II	41 (53.9)	26 (65.0)	
III	31 (40.8)	11 (27.5)	
Stage, <i>n</i> (%)			0.041
I	16 (21.5)	2 (5.0)	
II	30 (32.9)	13 (32.5)	
III	28 (40.8)	17 (42.5)	
IV	2 (3.9)	8 (5.0)	
Metastatic sites, <i>n</i> (%)			0.312
Lymph nodes	11 (14.5)	12 (30.0)	
Bone	39 (51.3)	23 (57.5)	
Visceral	35 (46.1)	18 (45.0)	
Number of metastatic sites, <i>n</i> (%)			0.022
1	56 (73.7)	21 (52.5)	
≥2	20 (26.3)	19 (47.5)	
DFS, months, <i>n</i> (%)			0.677
≤24	23 (30.3)	14 (35.0)	
>24	53 (69.7)	26 (65.0)	

DFI, disease-free interval.

ed with chemotherapy. The baseline characteristics of patients are summarized in Table 2. The median age was 58 years in the NCT group and 54 years in the CT group. The highest DFS period was >24 months in both NCT and CT groups. There were no statistically significant differences in HR/HER2 status, histological grade, tumor stage, and metastatic sites (lymph nodes, bone, and visceral metastatic sites). However, there were more patients with 2 or more metastatic sites in the CT group than in the NCT group (47.5 and 26.3%, respectively).

Clinical Outcomes and Safety

The median PFS for all patients was 10 months (Fig. 1A). Patients receiving first-line fulvestrant had better metastatic PFS (mPFS) than those receiving second-line fulvestrant (12 vs. 6 months; $p = 0.000$; Fig. 1B). NCT patients had better PFS than CT patients (16 vs. 8 months;

Fig. 1. Kaplan-Meier curves for progression-free survival probabilities for all enrolled 116 patients (A), stratified by fulvestrant lines (B) and previous treatment (C).

$p = 0.007$; Fig. 1C). Subgroup analysis showed that among patients with a shorter DFS (≤ 24 months), NCT patients had a significantly longer PFS than CT patients ($p = 0.009$; Fig. 2A). However, in patients with a longer DFS (> 24 months), the PFS was similar between the NCT and CT groups ($p = 0.110$; Fig. 2B).

PFS was significantly longer in the NCT group than in the CT group among patients without visceral metastasis ($p = 0.008$; Fig. 2D). However, there were no significant differences in PFS between the 2 groups among patients with bone metastasis ($p = 0.085$; Fig. 2C). Among patients with one metastasis site, the PFS was longer in NCT patients than in CT patients ($p = 0.025$; Fig. 2E). In patients with 2 or more metastasis sites, the mPFS of the CT group was longer than that of the NCT group (Fig. 2F), although the difference did not reach statistical significance ($p = 0.135$).

In the multivariate Cox model, the choice of chemotherapy before fulvestrant treatment was an important factor for PFS (Table 3). The results indicated that in patients with a longer DFS, without visceral metastasis, or one metastasis site, omitting chemotherapy before fulvestrant treatment was a beneficial factor.

Treatment Safety

The grade 3/4 adverse events are summarized in Table 4. Hematological toxicities and nausea were significantly more frequent in the CT group than in the NCT group (12.5 vs. 1.3% and 15 vs. 1.3%, respectively; $p < 0.05$). Hand-foot syndrome, atrial fibrillation, and increased alanine aminotransferase were only observed in the CT group (7.5 vs. 0%). Oral mucositis and myalgia, arthralgia, and hot flushes occurred in both groups.

Discussion

HR-positive breast cancer is the most common subtype in both young and old women. ET is the mainstay of treatment for HR-positive postmenopausal advanced breast cancer patients. Compared with AI, fulvestrant is currently the preferred standard first-line therapy for HR-positive postmenopausal women with MBC.

Similarly, in our study, 116 (85.9%) patients received fulvestrant as first-line ET, and 19 (14.1%) patients received fulvestrant as the second line or later lines of ET. Even though there were no significant differences in clinical features, there was a little difference. Our study showed that patients with later stage and worse grade received fulvestrant as the second-line treatment. We think reasons may be as follows: first, most doctors think that patients with later stage and worse grade should firstly receive chemotherapy. The maintenance treatment with AI or NSAI drugs are sufficient after chemotherapy. Second, the price of fulvestrant is higher than that of AI or NSAI. Some patients chose fulvestrant as the second-line treatment. Third, the sample is small, especially the patients who received fulvestrant as the second-line treatment. There was some selection bias.

In daily clinical practice, switching to ET during or after chemotherapy is a common strategy that is used for maintaining efficacy and decreasing the incidence of side effects. Such a strategy is also supported by the European Consensus Guidelines with a level of evidence of IC (class I/C level) [11]. In China, physicians recommend first-line chemotherapy for younger patients with late stage disease and 2 or more metastatic sites. This was also reported by Dufresne et al. [12], who showed that patients with lymph node-positive disease, multiple metastatic sites, and a lon-

Fig. 2. Kaplan-Meier curves for progression-free survival probabilities stratified by previous treatment in patients with different disease-free survival (**A**, **B**), bone metastasis (**C**), without visceral metastasis (**D**), with 1 metastasis site (**E**), and with 2 or more metastasis sites (**F**). NCT, metastatic breast cancer patients during disease progression did not receive chemotherapy treatment; CT, metastatic breast cancer patients received chemotherapy treatment before fulvestrant treatment during disease progression.

ger disease-free interval usually receive chemotherapy as the first-line treatment and ET as the maintenance treatment. Because the risk of recurrence is higher in these patients, they should receive chemotherapy firstly to prevent recurrence or metastasis progression. In addition, doctors tend to directly choose ET for patients with a lower tumor burden and a better prognosis and for patients with bone-only metastasis [13]. Lobbezoo et al. [14] performed a retrospective analysis and reported that bone-only metastasis should be an indication for an ET-first approach. Nikura et al. [15] demonstrated that ET is not inferior to chemotherapy in HR+/HER2- MBC patients with bone-only metastasis. Consistent with these findings, the CT group in this study included a greater number of patients with a higher tumor burden (later stage and 2 metastasis

sites). Our study showed that most Chinese doctors prefer to choose chemotherapy as first treatment for patients with a higher tumor burden and then switching to ET.

In this study, the mPFS for all users, first-line users, and second users was 10, 12, and 6 months, respectively. The mPFS for first-line users in our study was shorter than the mPFS reported in clinical trials. The FALCON trial showed that fulvestrant significantly improved the PFS (mPFS, 16.6 months) for patients with HR-positive locally advanced or metastatic breast cancer who did not receive previous ET [10]. The mPFS in patients receiving second-line fulvestrant in this study was similar to that reported in clinical trials. The CONFIRM phase 3 trial enrolled 735 HR-positive advanced breast cancer patients who experienced progression after prior ET from 17 coun-

Table 3. Cox proportional hazard analysis of influence on progression-free survival

Variables	Hazard ratio	95% CI	<i>p</i> value
Age			
<60 years	reference		
≥60 years	0.990	0.423–2.371	0.982
Tumor grade			
I	reference		
II	1.700	0.474–6.097	0.415
III	2.179	0.798–5.000	0.066
Tumor stage			
I	reference		
II	1.660	0.162–17.013	0.669
III	1.045	0.110–9.903	0.969
IV	0.763	0.082–7.094	0.812
ER status			
Negative	reference		
Positive	0.372	0.066–2.095	0.262
PR status			
Negative	reference		
Positive	1.252	0.472–3.322	0.652
HER2 status			
Unknown	reference		
Negative	1.384	0.190–10.087	0.749
Positive	1.270	0.449–3.588	0.593
DFS, months			
≤24	reference		
>24	0.488	0.209–1.142	0.098
Metastatic sites			
1	reference		
≥2	1.123	0.432–4.321	0.538
Bone metastasis			
No	reference		
Yes	1.244	0.455–3.403	0.670
Visceral metastasis			
No	reference		
Yes	1.454	0.494–4.279	0.497
CT before			
No	reference		
Yes	2.225	1.097–4.510	0.027

tries. The results showed that fulvestrant 500 mg improved the clinical benefit in MBC patients previously treated with ET. The mPFS was 6.5 months in this trial [8]. This could be attributed to the fact that most patients in the FALCON trial did not receive any treatment including neoadjuvant and adjuvant treatment. In this study, most patients received adjuvant ET, and ET may not be effective in these patients. The present study and clinical trials suggested that the early administration of fulvestrant was associated with better patient prognosis. In addition, after multiline ET, the ER status may change, which may lead to the development of drug resistance. Similarly, our study suggested that HR-positive MBC patients should receive fulvestrant treatment as early as possible.

Several clinical studies demonstrated the efficacy and safety of fulvestrant treatment and proposed that fulves-

Table 4. Treatment-related adverse events

Adverse event (grade 3/4)	NCT (<i>n</i> = 76), <i>n</i> (%)	CT (<i>n</i> = 40), <i>n</i> (%)
Leukopenia	0 (0)	4 (10)
Trombocytopenia	0 (0)	0
Anemia	1 (1.3)	1 (2.5)
Hand-foot syndrome	0 (0)	1 (2.5)
Atrial fibrillation	0 (0)	1 (2.5)
Alanine aminotransferase increased	0 (0)	1 (2.5)
Oral mucositis	2 (2.6)	1 (2.5)
Myalgia, arthralgia	6 (7.9)	1 (5)
Hot flushes	23 (30.2)	11 (27.5)
Nausea	1 (1.3)	6 (15)

trant should be the first-line therapy for MBC patients because these patients have a relatively good prognosis compared with those receiving multiline therapy [16, 17]. In these trials, the rate of patients who received chemotherapy was low. In the FALCON trial, one third of the patients had previously received CT. However, in clinical practice in China, HR-positive MBC patients usually first receive chemotherapy before receiving ET. Dufresne et al. [12] examined the efficacy of chemotherapy (capecitabine) compared with hormonal therapy after response to first-line chemotherapy in patients with HR-positive and HER2-negative breast cancer. They found that hormonal therapy can improve the time to progress over chemotherapy (13 vs. 8 months; *p* = 0.011). In addition, patients in the hormonal therapy group had fewer adverse events, whereas patients in the MCT group experienced grade 3–4 adverse events [18]. Another study showed that patients with HR+ HER2– MBC receiving maintenance hormonal therapy had a long PFS and overall survival after first-line chemotherapy (16.3 and 48.8 months, respectively) [12].

Whether HR-positive MBC patients should directly receive fulvestrant treatment or receive maintenance fulvestrant treatment after chemotherapy for first-line ET remains unclear. An Italian clinical study showed that patients with de novo metastatic disease have a relatively good prognosis compared with those with recurring disease. However, there was no difference in mPFS between patients receiving fulvestrant treatment at progressive disease or those receiving fulvestrant as maintenance after chemotherapy (11.6 and 11.1 months, respectively) [19]. This result was slightly different from those of the present study. The present study examined the efficacy of prefulvestrant treatment in ER+/HER2– MBC patients in China. The results showed that the NCT group had a longer PFS than the CT group. This can be explained as follows: first, many patients had 2 and more metastatic sites in the CT group. The prognosis of these patients is usually worse. Second, there were few patients with de novo metastatic

disease in our study, and most of them received adjuvant chemotherapy or adjuvant endocrine therapy. Our result indicated that the prognosis was better for patients firstly receiving fulvestrant treatment at progressive disease than those receiving fulvestrant as maintenance after chemotherapy. In other words, the earlier fulvestrant is used, the better prognosis patients would have.

Bone metastasis is the most common site in HR-positive breast cancer patients [20]. A recent analysis confirmed that breast cancer patients with bone-only metastasis have a better PFS and a good response to ET [21]. However, bone-only disease is not as common, and it is often studied in combination with other visceral sites or lymph nodes in clinical practice. In this study, there were few patients with bone-only metastasis, and most patients had bone metastasis together with visceral sites or lymph node metastasis. We found no differences in the NCT group and CT group between those with or without bone metastasis. One reason for this result could be that most patients have a combination of bone and non-bone metastatic sites. The prognosis of these patients is poor, and they show a poor response to ET. However, patients without visceral metastases are often better likely to respond to ET than those with visceral metastases. In the FALCON study [10], the mPFS was longer in patients without visceral disease than in those with visceral disease (22.3 and 13.8 months, respectively) after first-line fulvestrant treatment [10, 11]. Similarly, in this study, the mPFS was longer in the NCT group than in the CT group in patients without visceral metastases. However, in patients with visceral metastases, the mPFS of the NCT group was slightly longer than that of the CT group (although not statistically significant). These findings indicated that for patients with visceral metastases and 2 or more metastatic sites, fulvestrant was suitable as the maintenance treatment after chemotherapy. However, for patients without visceral metastases, the prognosis was better to receive fulvestrant treatment after disease progression.

The present study had several limitations. First, this study had a retrospective design. The critical issue addressed was which patients should receive fulvestrant directly and which ones should be treated with maintenance fulvestrant. This question remained unanswered because we did not perform a clinical trial. Second, there was some selection bias because data were derived from a single institution and the number of patients was too small to draw firm conclusions.

Conclusion

The earlier fulvestrant is used for advanced breast cancer patients, the better prognosis patients would have. Fulvestrant first-line users had a median PFS of 12 months

which was longer than that of the second-line users (6 months). Most Chinese doctors prefer to choose chemotherapy as first treatment for patients with a higher tumor burden and switching to ET. In addition, patients with a shorter DFS, 1 metastasis site and without visceral metastasis should receive fulvestrant treatment as soon as possible after disease progression. However, patients with 2 or more metastasis sites could receive chemotherapy as first treatment and switch to ET.

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Statement of Ethics

The study protocol has been approved by the Affiliated Hospital of Qingdao University on human research. All subjects have given their written informed consent.

Disclosure Statement

We have no conflicts of interest to disclose.

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Author Contributions

M.L.: data analysis, interpretation of data, drafting article. T.M.: data collection. Y.M.: interpretation of data and writing assistance. Y.W.: data collection and data analysis. X.L.: literature search. Y.S.: study concept and design. H.W.: publication decision.

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