Original Study

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Fulvestrant 500 mg Versus Exemestane in Postmenopausal Women With Metastatic Breast Cancer Resistant to Adjuvant Nonsteroidal Aromatase Inhibitors in Clinical Practice: A Multicenter Retrospective Study

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Abstract

There is no direct comparison of fulvestrant 500 mg and exemestane among metastatic estrogen receptor-positive (ER^+) breast cancer patients. This retrospective study enrolled 120 patients in China. We found that fulvestrant 500 mg showed better efficacy than exemestane in first-line therapy for metastatic breast cancer of ER^+ postmenopausal women after adjuvant nonsteroidal aromatase inhibitor treatment failure.

Background: Fulvestrant 500 mg and exemestane are widely used agents in first-line therapy for metastatic breast cancer (MBC) of estrogen receptor (ER)-positive (ER^+) postmenopausal MBC after failure of adjuvant nonsteroidal aromatase inhibitor (NSAI) treatment. Although fulvestrant 250 mg had similar efficacy compared with exemestane (Evaluation of Faslodex versus Exemestane Clinical Trial study) and fulvestrant 500 mg was superior to fulvestrant 250 mg (Comparison of FASLODEX In Recurrent or Metastatic Breast Cancer study), no direct comparison between fulvestrant 500 mg and exemestane has been conducted. The aim of this study was to compare the efficacy and safety of fulvestrant 500 mg and exemestane in daily practice. **Patients and Methods:** We retrospectively evaluated the medical records of all patients with ER^+ $HER2^-$ MBC who received fulvestrant 500 mg or exemestane 25 mg as first-line therapy for MBC from 2015 to 2017 in 4 institutions. A total of 120 patients were available for analysis. Both agents accounted for 50% (60) patients. **Results:** The median progression-free survival (PFS) of the fulvestrant group was significantly longer than that in the exemestane group (6.2 months [95% confidence interval (CI), 5.0-7.4] versus 4.8 months [95% CI, 3.0-6.7], $P = .024$). In subgroup analysis, for patients with visceral metastasis or primary endocrine resistance, no significant difference considering PFS was observed in the 2 groups ($P = .563$ and .769). No significant difference of Grade 3/4 adverse events was observed in the 2 groups (3 patients, 5% versus 2 patients, 3.3%; $P = .648$). **Conclusion:** Fulvestrant 500 mg showed better efficacy than exemestane in first-line therapy for MBC of ER^+ postmenopausal women after failure of adjuvant NSAI treatment. For patients with visceral metastasis or primary endocrine resistance, both treatments showed poor outcomes, indicating a need for further alternatives (targeted therapy or chemotherapy). Both agents were well tolerated in terms of toxicities.

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Keywords: ER^+ $HER2^-$ breast cancer, Endocrine sensitivity, Endocrine therapy, Fulvestrant, Metastatic breast cancer

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Introduction

Breast cancer (BC) remains the most common malignancy and a huge cause of death in women worldwide, leading to nearly 1.8 million new cases and 464 thousand deaths per year, mostly for metastatic BC (MBC).[1] In China, the incidence and mortality of BC keeps growing according to the latest data.[2]

Hormone receptor (HR)-positive (HR^+) BC includes nearly 70% of all BC patients.[3] For HR^+ $HER2^-$ MBC, endocrine therapy is the first and foremost treatment choice if patients have no symptomatic visceral metastasis, aggressive diseases, or endocrine therapy resistance after progression with adjuvant nonsteroidal aromatase inhibitor (NSAI) treatment.[4] Fulvestrant (Ful) is a selective estrogen receptor (ER) downregulator. It works by downregulating and by degrading the ER. Exemestane (Exe) is a steroidal aromatase inhibitor (SAI), also widely used in MBC patients after adjuvant NSAI.[5]

In the EFECT study (Evaluation of Faslodex versus Exemestane Clinical Trial), 250 mg Ful showed similar efficacy compared with Exe in terms of median time to progression (3.7 months vs. 3.7 months; $P = .653$).[6] In a phase III CONFIRM (Comparison of FASLODEXIn Recurrent or Metastatic Breast Cancer) study, 500 mg Ful was proved to perform better than 250 mg Ful in ER^+ MBC patients pretreated with aromatase inhibitors (AI) considering median progression-free survival (mPFS; 6.5 months vs. 5.5 months; $P = .006$).[7] The SoFEA study (Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer) compared Ful 250 mg, Ful 250 mg and anastrozole (Ana), and Exe, and showed similar efficacy among the 3 groups.[8] However, there is no direct comparison between these 2 agents after disease progression with NSAI treatment.

Although some research showed poor efficacy of SAI after NSAI because of an estrogen receptor alpha mutation,[9,10] specific comparisons between Ful 500 mg and Exe remains unknown. Moreover, which agent is more popular in daily practice? This study aimed to determine the performance of Ful 500 mg and Exe in HR^+ $HER2^-$ MBC patients after progression of disease with adjuvant NSAI treatment in clinical practice.

Patients and Methods

Patients and Treatments

We analyzed patients diagnosed with MBC between 2014 and 2017 at 4 institutions including: Fudan University Shanghai Cancer Center; The Second Affiliated Hospital of Medical College, Xi'an Jiaotong University; Jiangsu Cancer Hospital; and Nanjing General Hospital. The eligibility criteria were as follows: (1) postmenopausal MBC patients who were confirmed as having an HR^+ $HER2^-$ negative tumor. ER and HR were considered "positive" when at least 1% of the nuclei was stained as determined using immunohistochemical (IHC) analysis. $HER2^-$ status were scored as 0 or +1 in IHC analysis or scored +2 if no amplification was found as a result of fluorescence in situ hybridization analysis; (2) relapse during adjuvant NSAI (letrozole/Ana) treatment or within the first year after at least 2 years duration of adjuvant NSAI treatment; (3) patients received Ful 500 mg or Exe 25 mg as first-line therapy for MBC, starting from 2014 to 2017. Those who received chemotherapy first for MBC were excluded. All data were retrospectively collected from medical records of individual institutions.

This study was approved by the Fudan University Shanghai Cancer Center Ethics Committee and institutional review boards for clinical investigation. All of the methods were performed in accordance with the 1964 Declaration of Helsinki and its later amendments, and the ethical standards of the institutional research committee. The study has been exempted from written informed consent as it's a retrospective study. Analysis and management was performed at the Fudan University Shanghai Cancer Center.

Outcome Measurements

The primary outcome measure of this investigation was progression-free survival (PFS), defined as time from initiation of Ful/Exe treatment to disease progression or death. The second outcome measures included overall survival (OS) and safety. OS was defined as time between initiation of treatment to death from any cause or censoring on July 20, 2018. Tumor evaluation was assessed according to Response Evaluation Criteria in Solid Tumors 1.1 criteria. Safety was evaluated as adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Disease-free interval (DFI) was defined as time from surgery to diagnosis of metastasis. Endocrine resistance was defined according to 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer consensus.[11]

Statistics

Clinicopathologic characteristics are summarized in descriptive statistics and compared between the 2 groups using the χ^2 test. Real-world practice of therapy options are described. Possible factors influencing the choice of treatment were evaluated using univariate and multivariate logistic regression. PFS and OS were estimated using the Kaplan–Meier method and compared using the log rank test. Hazard ratios with 2-sided 95% confidence interval (CI) were calculated with unadjusted and adjusted Cox proportional hazards models for group comparisons. Prognostic factors regarding PFS and OS in different subgroups were investigated using a Cox regression model with 95% CI in univariate and multivariate models. Subgroup analysis was done using the Cox regression model and shown in a forest plot. A P value $< .05$ was considered statistically significant. All statistical analyses were managed using SPSS version 23.0 (IBM Corp, Armonk, NY). The forest map was made using GraphPad Prism version 7.0 (GraphPad Software, San Diego, CA).

Availability of Data and Materials

The data sets generated and/or analyzed during the current study are not publicly available because of hospital policy but are available from the corresponding author upon reasonable request.

Results

Patients and Treatments

The medical records of a total of 216 patients from 4 hospitals who used Ful or Exe were retrospectively reviewed and 125 patients met the inclusion criteria. Five patients were excluded because of incomplete medical history. Thus, 120 patients were included for evaluation.

Table 1 Baseline Characteristics of Patients Grouped According to Fulvestrant or Exemestane Treatment

Characteristic	Fulvestrant (n = 60)	Exemestane (n = 60)	*P*
Median Age (Range)	58 (38-71)	61 (33-85)	.61
DFI			.559
≤2 Years	18 (30)	21 (35)	
>2 Years	42 (70)	39 (65)	
ECOG PS Score			.648
0-1	58 (96.7)	57 (95)	
≥2	2 (3.3)	3 (5)	
Number of Metastatic Sites			.128
1	21 (35)	26 (43.3)	
2	17 (28.3)	22 (36.7)	
≥3	22 (36.7)	12 (20)	
Metastatic Site Location			
Visceral	28 (46.7)	33 (55)	.361
Liver	8 (13.3)	16 (26.7)	.109
Lung	21 (35)	22 (35)	.84
Bone only	17 (28.3)	18 (30)	.841
Adjuvant Endocrine Therapy			1
Letrozole	39 (65)	39 (65)	
Anastrozole	21 (35)	21 (35)	
Endocrine Sensitivity			.133
Primary resistant	27 (45)	19 (31.7)	
Secondary resistant	33 (55)	41 (68.3)	

Data are presented as n (%) except where otherwise noted.
Abbreviations: DFI = disease-free interval; ECOG = Eastern Cooperative Oncology Group; PS = performance status.

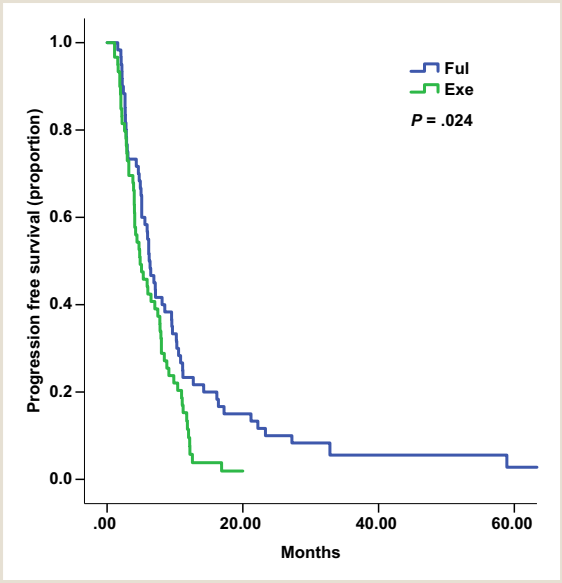
Among the 120 patients, 60 (50%) patients received Ful 500 mg and 60 (50%) patients received Exe. Patient and disease characteristics at baseline between the 2 treatment groups are shown in Table 1. The median age was 58 years for the Ful group and 61 years for the Exe group.

Most patients were in good status (Eastern Cooperative Oncology Group performance status of 0-1). Visceral metastases accounted for 28 (46.7%) and 33 (55%) of patients in Ful and Exe group, respectively. Of patients in the Ful group, 17 (28.3%) and 18 (30%) of Exe group had bone-only disease. Adjuvant endocrine therapy of letrozole was used in 39 (65%) of patients and Ana for 21 (35%) of patients in both groups. Patients with primary endocrine resistance had a trend of receiving more Ful than Exe ($P = .13$).

Treatment Efficacy

With a median 28-month follow-up, 57 of 60 patients in both groups experienced progressive disease. The mPFS of the Ful group was significantly longer than that in the Exe group (6.2 months [95% CI, 5.0-7.4] vs. 4.8 months [95% CI, 3.0-6.7]; $P = .024$; Figure 1). The median OS was not reached at the time of analysis.

Figure 1 Kaplan–Meier Curves for Progression-Free Survival According to Treatment Arm



Abbreviations: Exe = exemestane; Ful = fulvestrant.

In subset analysis, the advantage of Ful over Exe was maintained across most of the subgroups. However, PFS of the Ful group was similar to that of the Exe group among patients with visceral metastasis (mPFS, 5.9 months vs. 4.7 months; $P = .561$) compared with those without visceral metastasis (mPFS, 7.1 months vs. 5.3 months; $P = .01$; Figure 2). Furthermore, patients with primary endocrine resistance had similar PFS in the Ful and Exe groups (mPFS, 5.9 months vs. 8.0 months; $P = .768$), compared with those with secondary endocrine resistance (mPFS, 7.1 months vs. 4.0 months; $P = .004$; Figure 2). The forest plot is shown in Figure 3.

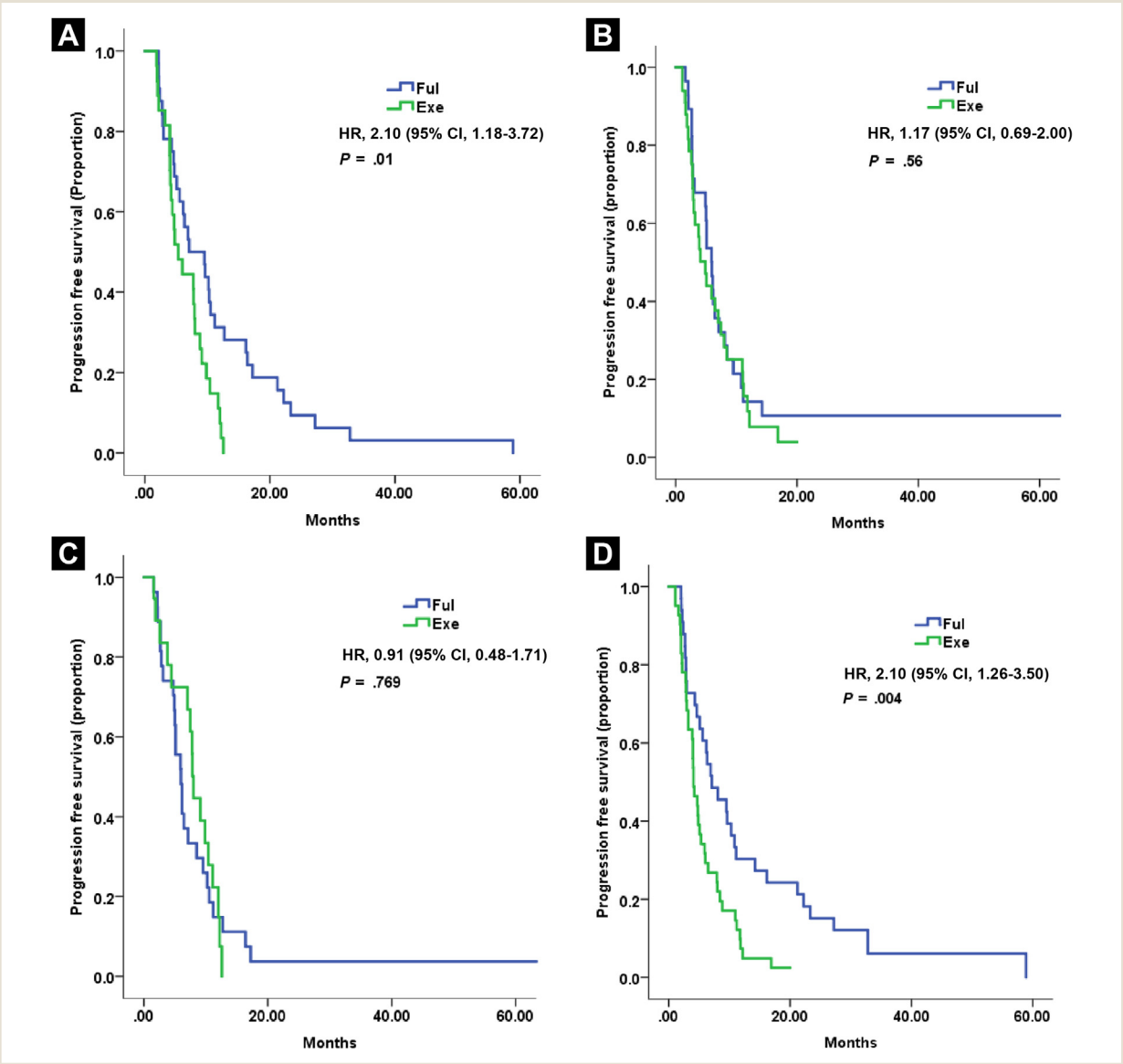
As for the prescription preference of Ful and Exe, no significant relation was found in the following factors: age ≥ or < 60 years, DFI > or ≤ 2 years, number of metastatic sites, visceral metastasis, liver metastasis, lung metastasis, adjuvant therapy, and endocrine sensitivity.

In univariate analysis, Ful therapy (hazard ratio, 0.643; 95% CI, 0.43-0.94; $P = .025$) and bone-only disease (hazard ratio, 0.042; 95% CI, 0.002-0.96; $P = .048$) were predictive of longer PFS. In terms of multivariate analysis, Ful therapy emerged as an independent prognostic factor even after balancing the age, DFI, number of metastatic sites, visceral metastasis, liver metastasis, lung metastasis, adjuvant therapy, and endocrine sensitivity. Ful therapy was associated with a lower risk of progression even after balancing the known factors (adjusted hazard ratio, 0.63; 95% CI, 0.43-0.94; $P = .023$).

Safety

Adverse events of Grade 3 or 4 are shown in Table 2. Ful and Exe were well tolerated in our study, with only 5% of Ful-treated patients and 3.3% of Exe-treated patients who endured Grade 3/4 AEs. No patient died as a result of a drug-related AE. Arthralgia, nausea or

Figure 2 Kaplan–Meier Curves for Progression-Free Survival According to Treatment Arm for Patients With (A) Nonvisceral Metastasis; (B) Visceral Metastasis; (C) Primary Endocrine Resistance; and (D) Secondary Endocrine Resistance



Abbreviations: Exe = exemestane; Ful = fulvestrant.

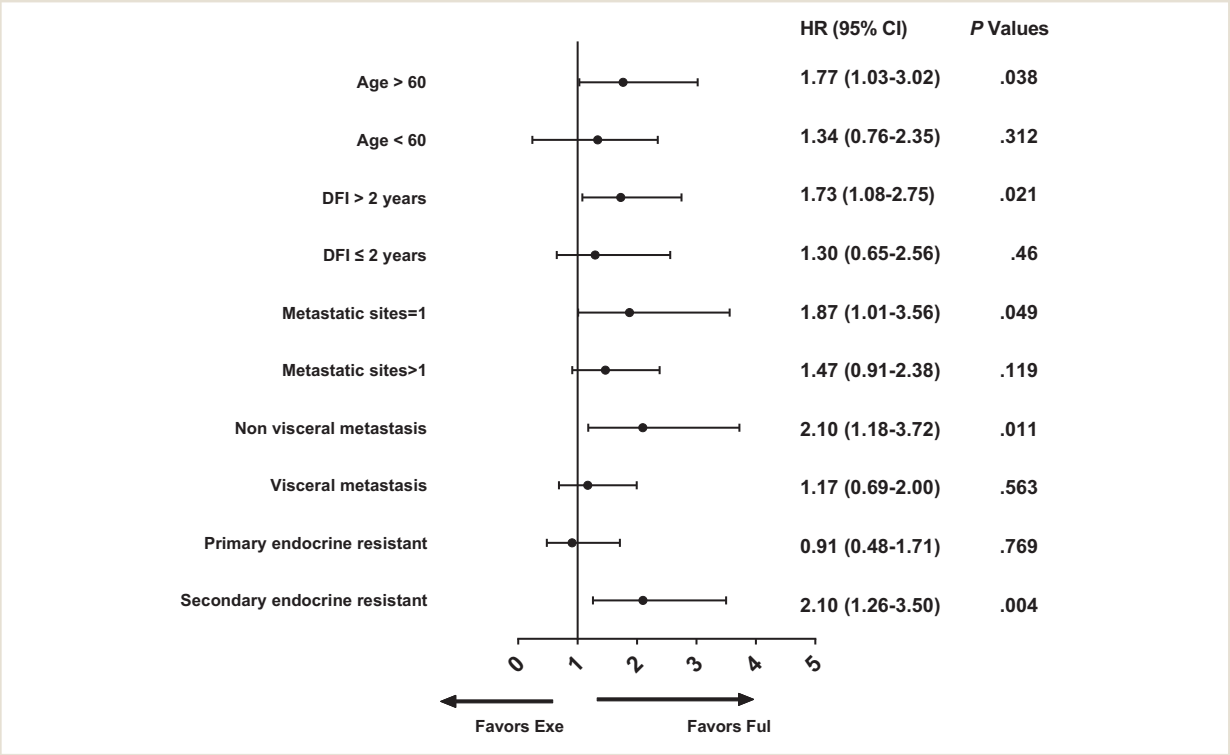
vomiting, and hot flush were observed once in the Ful group. Chest pain and fracture were observed once in the Exe group. In all, no significant difference of Grade 3/4 AEs was observed in the 2 groups (3 patients, 5% vs. 2 patients, 3.3%; $P = .648$).

Discussion

In this study, we examined the daily practice of 500 mg Ful versus Exe in HR^+ $HER2^-$ MBC patients after failure of adjuvant NSAI treatment in China. To the best of our knowledge, this is the first direct investigation of the comparison between 500 mg Ful and Exe in MBC patients who relapsed during adjuvant NSAI treatment.

First, data showed that a similar number of patients received Ful or Exe (50% vs. 50%) after adjuvant NSAI treatment. Furthermore, the prescription of 2 treatments were not related to known baseline factors. This phenomenon indicated that both treatments were commonly used in clinical practice without specific selection of patients. In real world data of the United States, 36.1% of patients received Ful and 42.3% received Exe after NSAI treatment,[5] which conformed to our study. It is also important to note that Ful had a higher price than Exe ($1500 vs. $200 per month in China at that time), thus some patients might not afford Ful. Moreover, no targeted therapy for ER^+ patients was approved in China until July, 2018, leading to fewer treatment options.

Figure 3 Forest Plot for Subgroup Analysis



Abbreviations: DFI = disease-free interval; Exe = exemestane; Ful = fulvestrant.

Our study revealed the superiority of 500 mg Ful over Exe in postmenopausal patients with ER^+ advanced BC after adjuvant NSAI treatment in terms of PFS. Previously, randomized controlled trials (RCT) showed similar efficacy of 250 mg Ful over Exe and better efficacy of 500 mg Ful over 250 mg Ful, as shown in Table 3. The EFECT trial[6] enrolled 493 ER^+ $HER2^-$ postmenopausal MBC patients pretreated with NSAIs and randomly divided them into 250-mg Ful and Exe groups, finally showing similar efficacy and safety of the 2 regimens. Another study, SoFEA, randomly assigned 723 MBC patients with NSAI resistance into 250 mg Ful, 250 mg Ful with Ana, Exe, and the result showed no difference in effectiveness among the 3 arms.[8] The CONFIRM study,[7] which compared 250 mg Ful and 500 mg Ful in 736 cases refractory to endocrine therapy, showed better efficacy of 500 mg Ful over 250 mg Ful in terms of PFS. The CHINA CONFIRM (Fulvestrant 500 mg vs 250 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer: a randomized, double-blind registrational trial in China) trial was designed as the CONFIRM study in China, and 221 MBC patients resistant to endocrine therapy were randomly divided into 500-mg Ful and 250-mg Ful groups, which, in the end showed results similar to the CONFIRM study.[12] On the basis of these RCT, 500 mg Ful and Exe are both recommended in the National Comprehensive Cancer Network (NCCN) guidelines and are widely used in clinical practice after failure of adjuvant endocrine therapy. A systemic review analyzed 7 RCTs comparing the efficacy and safety of Ful with 3 AIs (Ana/letrozole/Exe) and showed that PFS for 500-mg Ful was significantly longer compared with AI (hazard ratio, 0.75; 95% CI, 0.62-0.91; $P = .003$),[13] which is consistent with our results. However, it did not balance the baseline factors as well as treatment lines, and the comparison included 3 agents (AIs) without specific comparisons of single regimens.

Table 2 Treatment-Related Grade3/4 Adverse Events

Adverse Event	Fulvestrant (n = 60), n (%)	Exemestane (n = 60), n (%)
Arthralgia	1 (1.7)	0
Nausea or Vomiting	1 (1.7)	0
Hot Flush	1 (1.7)	0
Chest Pain	0	1 (1.7)
Fracture	0	1 (1.7)
All	3 (5)	2 (3.3)

In the exploratory subgroup analysis, we found that the superiority of Ful over Exe was not obvious in patients with primary endocrine resistance or visceral metastasis. Primary endocrine resistance is defined as relapse of disease within 2 years of adjuvant endocrine therapy. These patients are considered poorly responsive to endocrine therapy. In NCCN guidelines, an alternative of chemotherapy could be recommended for them. However, we found that another line of endocrine therapy was still used in

Table 3 Randomized Controlled Trials That Have Shown Similar Efficacy of 250 mg Ful Over Exe and Better Efficacy of 500 mg Ful Over 250 mg Ful

Trial/Year	Phase	Previous	Treatment	Size	TTP/PFS, Months	OS, Months
EFECT/2008	III	NSAI	Ful 250 mg Exe	351 342	3.7 $P > .1$ 3.7	NA
SoFEA/2013	III	NSAI	Ful 250 mg with Ana Ful 250 mg Exe	243 231 249	4.4 $P > .1$ 4.8 3.4	20.2 $P > .1$ 19.4 21.6
CONFIRM/2010	III	TAM, NSAI	Ful 250 mg Ful 500 mg	374 362	5.6 $P = .006$ 5.5	22.3 $P = .016$ 26.4
CHINA CONFIRM/2016	III	TAM, NSAI	Ful 250 mg Ful 500 mg	110 111	4.0 $P = .078$ 8.0	NA

Abbreviations: Ana = anastrozole; CHINA CONFIRM = Fulvestrant 500 mg vs 250 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer: a randomized, double-blind registrational trial in China; CONFIRM = Comparison of FASLODEXIn Recurrent or Metastatic Breast Cancer; EFECT =Evaluation of Faslodex versus Exemestane Clinical Trial; Exe = exemestane; Ful = fulvestrant; NSAI = nonsteroidal aromatase inhibitor; PFS = progression-free survival; SoFEA = Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer; TAM = tamoxifen; TTP = time to progression.

clinical practice, indicating a preference for endocrine therapy. As for patients with visceral metastasis, we think that comparatively extensive metastasis and large tumor burden led to quick progression of disease. This trend was also seen in the phase III FALCON (Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer) trial, which compared the efficacy of 500 mg Ful with Ana in patients with locally advanced or metastatic HR^+ BC who had not previously received endocrine therapy.[14] In the visceral disease subgroup, the hazard ratio was 0.99 (95% CI, 0.74-1.33) for PFS with 500 mg Ful versus Ana (15.9 months vs. 13.8 months), whereas the hazard ratio was 0.59 (95% CI, 0.42-0.84) in the nonvisceral metastasis group, suggesting a lower benefit from Ful in patients with visceral metastasis.

Bone-only metastasis was found to be a predictor of longer PFS in univariate analysis. Another study of pooled analysis enrolled 13 trials with 10,521 MBC patients, and showed results of better PFS of patients with bone-only disease compared with those with no bone metastasis at baseline (hazard ratio, 0.70; 95% CI, 0.65-0.76) and bone with other lesions at baseline (hazard ratio, 0.64; 95% CI, 0.591-0.696),[15] which was consistent with our findings.

With regard to toxicity, both agents were well tolerated. Grade 3/4 AEs occurred only in 5% of patients for Ful and 3.3% patients for Exe. Interestingly, we observed 2 rare Grade 3/4 AEs in the Exe group: chest pain and lower limb fracture. We thought the chest pain was noncardiac chest pain, which was caused by intercostal muscle pain, also reported in the SoFEA study.[8] Lower limb fracture was regarded as a result of bone loss because of long-term use of Exe. A substudy of the MAP.3 (a randomised, placebo-controlled, double-blind trial of exemestane 25 mg a day for the primary prevention of breast cancer) trial reviewed 351 postmenopausal women randomly given Exe or placebo and showed that 2 years of treatment with Exe worsens age-related bone loss in postmenopausal women.[16] This AE reminds doctors of the importance of monitoring bone density and give calcium and vitamin D supplementation for postmenopausal patients using Exe.

In conclusion, this study revealed the clinical practice of 500 mg Ful and Exe for ER^+ $HER2^-$ MBC patients who relapsed during adjuvant NSAI treatment. Both agents accounted for 50% of the patients. The efficacy of 500 mg Ful exceeded Exe in terms of PFS. In addition, for patients with visceral metastasis or primary endocrine resistance, both agents performed poorly for outcomes, suggesting a need for further therapy. Bone-only disease indicated longer PFS. Patients had good tolerance to both agents, however, Exe-related fracture because of bone loss requires vigilance.

In our study, all consecutive BC patients who met our criteria were enrolled, however, because of the limited time since Ful has been on the market in China (2014), the sample size is limited. Second, although we suggest patient visits approximately every 2 months, the frequency of follow-up visit might vary a bit, and we did not have blinded imaging evaluation, which could affect the results. However, it also reflected the real world situation. Recall bias might exist in the record of AEs. Moreover, the evidence level of a retrospective study is insufficient.

Because this study was retrospective, a RCT is needed for further evidence. It is worth waiting for results of an ongoing RCT (NCT02646735) focused on these 2 agents. With the development of targeted therapy, the sequential use and choice of endocrine therapy or combined therapy should be carefully evaluated for the best benefit of BC patients.

Conclusion

Fulvestrant 500 mg showed better efficacy than Exe in first-line therapy for postmenopausal patients with ER^+ MBC after failure of adjuvant NSAI treatment. For patients with visceral metastasis or primary endocrine resistance, both treatments showed poor outcomes, indicating a need for further alternatives (for example, targeted therapy or chemotherapy). Both agents were well tolerated in terms of toxicities, whereas Exe-related fracture because of bone loss requires vigilance.

Clinical Practice Points

- In a real-world setting, patients received Ful and Exe equally after NSAI in China.
- In general, Ful showed better efficacy than Exe after adjuvant NSAI treatment failure.
- In patients with visceral metastasis or primary endocrine resistance, both agents showed poor outcome.
- Both agents were well tolerated.

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Disclosure

The authors have stated that they have no conflicts of interest.

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