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Multicenter Observational Study of Fulvestrant 500 mg in Postmenopausal Japanese Women with Estrogen Receptor-Positive Advanced or Recurrent Breast Cancer after Prior Endocrine Treatment (SBCCSG29 Study)

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Background: Fulvestrant 500 mg has been an option for endocrine therapy for advanced or recurrent breast cancer after prior endocrine treatment since November 2011 in Japan. This study aimed to clarify the effectiveness and safety of fulvestrant 500 mg in clinical settings.

Methods: This was a multicenter, both prospective and retrospective, observational study of 132 postmenopausal women (median age 66) with locally advanced or metastatic breast cancer, who had been treated with fulvestrant. Information from medical records was retrospectively obtained from 9 hospitals (Saitama Breast Cancer Clinical Study Group: SBCCSG) in Saitama prefecture, Japan, from October 2012 to April 2014. The primary end point was time to treatment failure (TTF). The secondary end points were overall survival (OS), objective response rate (ORR), clinical benefit rate (CBR), and adverse events (AE) (CTCAE ver. 4). The choice of subsequent therapy after fulvestrant was also evaluated.

Results: The median TTF was 6.1 months. Median OS was 28.5 months (the starting date was the first day of fulvestrant). ORR was 12.9% and CBR was 45.5%. The most common AEs were injection site reactions (9.1%). The rate of grade 3 AE was only 2.3% (3/132). The number of patients who underwent subsequent therapy after fulvestrant were 54 (55.7%) receiving chemotherapy, 42 (43.3%) receiving non-fulvestrant endocrine therapy, and 1 (1%) receiving mammalian target of rapamycin inhibitor (mTORi) + endocrine therapy (ET).

Conclusion: Fulvestrant 500 mg is an effective and safe treatment for patients with advanced or recurrent breast cancer after prior endocrine treatment. (J Nippon Med Sch 2019; 86: 165–171)

Key words: fulvestrant, advanced/relapsed breast cancer, cohort study, Japanese

Introduction

In patients with advanced and recurrent estrogen receptor (ER)-positive breast cancer, endocrine therapy is less toxic than cytotoxic agents and thus contributes to quality of life. Fulvestrant is a pure anti-estrogen with no agonistic actions, which blocks dimerization of the estrogen-ER complex and down-regulates the ER. At a dose of 250 mg, fulvestrant is at least as effective as anas-

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Table 1 Clinical characteristics of patients

Characteristics	n = 132
Age at fluvestrant start, years	
Median	66
Range	47-96
BMI	
Median	23.3
Range	16.3-38.8
Clinical presentation, n (%)	
Advanced	23 (17.4)
Relapsed	109 (82.6)
Histology, n (%)	
Invasive ductal carcinoma	120 (90.9)
Invasive lobular carcinoma	4 (3.0)
Other type	3 (2.3)
Unknown	5 (3.8)
Hormone receptor status (primary tumor), n (%)	
ER-positive/-negative/unknown	122 (92.4)/4 (3.0)/6 (4.5)
PR-positive/-negative/unknown	95 (72.0)/30 (22.7)/7 (5.3)
HER2 status (primary tumor), n (%)	
HER2-positive/-negative/unknown	22 (16.7)/78 (59.1)/32 (24.2)

BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, human epithelial growth factor receptor 2

trozole and exemestane for second-line treatment of postmenopausal hormone-positive advanced breast cancer[1,2]. In the phase III CONFIRM trial, which compared doses of fulvestrant (250 mg every 28 days vs 500 mg, on days 0, 14, 28, and every 28 days thereafter) in postmenopausal women with ER-positive, locally advanced or metastatic breast cancer for disease relapse, or disease progression after treatment with an aromatase inhibitor, fulvestrant 500 mg was associated with statistically significant increases in progression free and overall survival and was not associated with greater toxicity than fulvestrant 250 mg[3,4]. Fulvestrant 500 mg has been an option for endocrine therapy for advanced or recurrent breast cancer after prior endocrine treatment since November 2011 in Japan. According to the current National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines, fulvestrant is one of the key drugs used, both alone and in combination with target monotherapy, for recurrent postmenopausal breast cancer or stage IV disease that is ER and/or progesterone receptor (PR) positive[5,6].

This study aimed to clarify the effectiveness and safety of fulvestrant 500 mg in clinical settings. We also focused on post-fulvestrant therapy.

Materials and Methods

This was a multicenter, both prospective and retrospective, observational study. Eligible patients were postmenopausal women with locally advanced or metastatic ER-positive breast cancer (histologically confirmed) who received treatment with fulvestrant (Faslodex®, AstraZeneca) 500 mg (days 0, 14, 28, and every 28 days thereafter) via intramuscular injection. Patients who had received prior endocrine therapies other than fulvestrant were eligible. Patients who would be prospectively registered, gave written informed consent before study inclusion. The presence of measurable lesions was not required for eligibility in this study. Patients were excluded if they had brain metastasis. Information from patients' medical records was retrospectively obtained from 9 hospitals (Saitama Breast Cancer Clinical Study Group: SBCCSG) in Japan. This study was approved by the Institutional or Central Ethics Committee.

Patients continued the treatment until disease progression, occurrence of unacceptable toxicities, drug withdrawal, patient request for withdrawal, or at the physician's discretion. The study was registered with the University Hospital Medical Information Network (UMIN number: 000009110). Time to treatment failure (TTF), overall survival (OS), clinical response, adverse events (AEs), and clinical response to subsequent post-fulvestrant therapy were investigated. The primary endpoint was TTF defined as the interval between the onset of study therapy and the termination of the therapy for

Table 2 Treatments for patients

Treatment line of fulvestrant, n (%)	132
Advanced	
2nd	2 (1.5)
≥3rd	19 (14.4)
Relapsed	
1st	19 (14.4)
2nd	19 (14.4)
≥3rd	73 (55.3)
Total number of previous therapies (include adjuvant therapy)	
Median (range)	4 (1-20)
1	7
2	20
3	18
4	32
5	21
≥6	34
Number of previous endocrine therapies for advanced or recurrent breast cancer	
Median (range)	2 (0-8)
0	21
1	30
2	31
3	28
≥4	22
Prior treatment just before fulvestrant, n (%)	
Endocrine therapy/chemotherapy/molecularly-targeted therapy	114 (86.4)/17 (12.9)/1 (0.8)
AI (letrozole/exemestane/anastrozole)	79 (36/28/15)
SERM (toremifen/tamoxifen)	29 (18/11)
Medroxyprogesterone acetate	6
Taxane (weekly PTX/bevacizumab+PTX/gemcitabine+PTX/docetaxel)	10 (5/2/2/1)
Fluoropyrimidine (capecitabine/capecitabine+cyclophosphamide/tegafur-uracil)	5 (2/2/1)
Others (cyclophosphamide/vinorelbine)	2 (1/1)
Trastuzumab	1
Subsequent post-fulvestrant therapies, n (%)	97
Endocrine therapy/chemotherapy/mTOR inhibitor	42 (43.3)/54 (55.7)/1 (1)
SERM (toremifen/tamoxifen)	19 (11/8)
AI (letrozole/exemestane/anastrozole)	13 (5/4/4)
Medroxyprogesterone acetate	8
Ethinyl estradiol	2
Fluoropyrimidine (capecitabine/S-1/capecitabine+lapatinib)	21 (14/5/2)
Taxane (weekly PTX/bevacizumab+PTX/docetaxel/docetaxel+cyclophosphamide)	18 (6/7/4/1)
Others (eribulin/vinorelbine)	13 (12/1)
Anthracycline (epirubicine+cyclophosphamide/THP-adriamycin)	2 (1/1)
Everolimus+exemestane	1

AI, aromatase inhibitor; SERM, Selective estrogen receptor modulator; PTX, paclitaxel

any reason, death due to the primary disease, or all-cause death. In patients who had measurable lesions, clinical responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1)[7]. Best overall response was determined based on the following criteria: complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD), and not evaluable (NE). Stable disease lasting 24 weeks was also defined as Long SD. The RECIST criteria were modified for this study. Tumor imaging interval and the modality for image evaluation were not prescribed. OS was defined as the interval between the onset of fulvestrant therapy and death. AEs were graded according to the National Cancer Institute the Common Terminology Criteria for Adverse Events Japanese version 4.0-Japan Clinical Oncology Group.

The choice of subsequent post-fulvestrant therapy was also investigated.

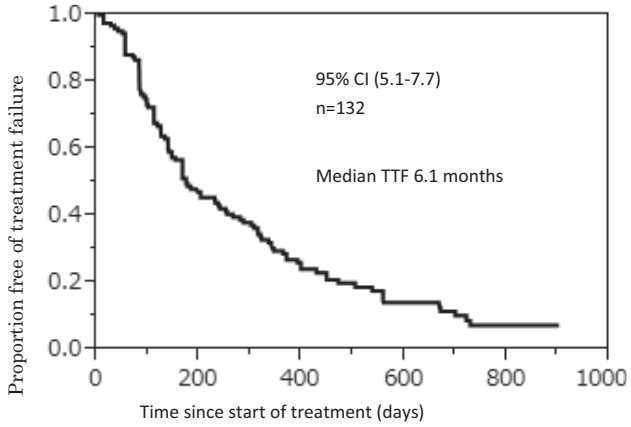

Fig. 1 Time to treatment failure with fulvestrant therapy with a median follow up of 18.4 months
TTF, time to treatment failure; CI, confidence interval

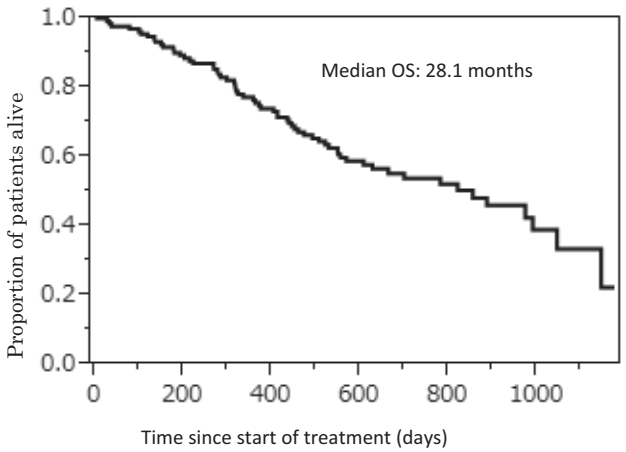

Fig. 2 Overall survival with fulvestrant therapy. At the time of completing data collection, 46.2% of patients (61/132) had died
OS, overall survival

The effectiveness of subsequent post-fulvestrant therapy was also evaluated using the modified RECIST, according to the primary physician's judgment.

Statistical Analyses

Statistical analyses were performed with JMP® version 10 (SAS Institute, Cary, NC, USA). TTF and OS distributions were estimated according to the Kaplan-Meier method.

Results

Patient Population

From October 2012 through April 2014, 132 postmenopausal women (prospective 3, retrospective 129) were recruited from 9 medical institutions of the Saitama Breast Cancer Clinical Study Group (SBCCSG).

Clinical characteristics of patients are shown **Table 1**. Median age was 66 years (range, 47–96 years). Median body mass index (BMI) was 23.3 (range, 16.3–38.3). Twenty-three patients (17.4%) had advanced breast cancer and 109 patients (82.6%) had relapsed breast cancer. In this study, all patients were confirmed to have evidence of ER sensitivity in primary and/or metastatic tumors. The numbers of ER-positive and PR-positive patients were 122 and 95, respectively. Only 22 patients had human epithelial growth factor receptor 2 (HER2)-positive breast cancer.

Primary endocrine therapy to be administered after recurrence was defined as first-line endocrine therapy[5]. If the relapse occurred while taking the first-line endocrine therapy, the patient was considered to be in a second-line category. If progressive disease was detected during the second-line endocrine therapy, third-line endocrine therapy was administered next. In this study, first use of fulvestrant for primary advanced breast cancer was excluded. Treatments of patients are shown in **Table 2**. In the treatment lines comprised of fulvestrant, the number of cases receiving advanced second-line treatment was 2 (1.5%), while 19 (14.4%) received more advanced treatments than second-line. The number of patients with relapsed breast cancer receiving first-line, second-line, and more than second-line treatments were 19 (14.4%), 19 (14.4%), and 73 (55.3%), respectively.

Ninety-two (69.7%) postmenopausal patients with advanced or recurrent breast cancer received fulvestrant as more than second-line treatment.

The numbers of patients with prior treatment just before fulvestrant administration were 114 (86.4%), 17 (12.9%), and 1 (0.8%) receiving endocrine therapy, chemotherapy, and trastuzumab, respectively. As subsequent post-fulvestrant treatment, 43.3% were given endocrine therapy, 55.7% chemotherapy, and 1% mammalian target of rapamycin (mTOR) inhibitor + endocrine therapy. The most commonly used post-fulvestrant chemotherapy was fluoropyrimidine (21.6%), which includes S-1 and capecitabine.

Efficacy

Median TTF was 6.1 months (95% CI: 5.1–7.7) (**Fig. 1**) and median OS was 28.5 months (95% CI: 18.7–34.4) (**Fig. 2**). At the data collection cut-off date of April 30, 2015, 46.2% of patients (61/132) had died.

Best overall response is shown in **Table 3**.

The ORR was 12.9%, including CR in 2.3% and PR in 10.6% of patients. The rate of long stable disease, i.e. SD for more than 24 weeks, was 32.6%. The CBR was 45.5%. Furthermore, fulvestrant was also active in subgroups of

Table 3 Best overall response in patients with metastatic or recurrent breast cancer who received fulvestrant

	n	CR	PR	LSD	SD	PD	NE	RR (%)	CBR (%)
All	132	3 (2.3)	14 (10.6)	43 (32.6)	18 (13.6)	51 (38.6)	3 (2.3)	12.9	45.5
Sites of metastasis or recurrence									
Local lesion	35	1	7	9	10	8	0	22.9	48.6
Lymph nodes	58	1	9	13	13	17	5	17.2	39.7
Lung	48	1	4	12	10	18	3	10.4	35.4
Liver	38	1	3	3	7	22	2	10.5	18.4
Bone	75	0	2	14	26	21	12	2.6	21.3
Skin/soft tissue	7	0	2	0	3	0	2	28.6	28.6
Pleura/pleural effusion	16	0	1	3	3	5	4	6.2	25.0
Peritoneum/ascites	4	0	0	0	3	1	0	0	0

CR, complete response; PR, partial response; LSD, long stable disease (SD>24 weeks); SD, stable disease;
PD, progressive disease; NE, not evaluable; RR, response rate=CR+PR; CBR, clinical response rate=CR+PR+LSD

Table 4 Treatment-related adverse events

	Grade†	
	1-3	>3
Any adverse events, n (%)	48 (36.4)	3 (2.3)
Injection site reaction	12 (10.0)	0
Hot flash	9 (6.8)	0
Joint disorder	7 (5.3)	0
Fatigue	7 (5.3)	0
Headache	2 (1.5)	0
Nausea	2 (1.5)	1
Constipation	2 (5.3)	0
Others	7 (5.3)	2*

†: Adverse events were graded according to the National Cancer Institute Common Terminology Criteria, version 4.03. *duodenal ulcer, cellulitis

patients with local lesions, lymph node involvement, and lung metastasis, yielding CBR of 48.6%, 39.7%, and 35.4%, respectively. The CBR of patients with liver metastasis was, however, only 18.4%.

Safety

AEs are shown in **Table 4**. The total number of AEs was 48 (36.4%). All of the AEs that developed during fulvestrant treatment had rates below 10%. The most common AE was injection site reaction, which occurred in 12 patients (9.1%). Grade 3 AEs developed in 3 patients (2.3%), one each with nausea, a duodenal ulcer, and cellulitis. There were no Grade 4 AEs in our study participants.

Selection of Post-Fulvestrant Therapy and Efficacy

The numbers of patients given subsequent therapy after fulvestrant, were 54 (55.7%), 42 (43.3%), and 1 (1%) receiving chemotherapy, non-fulvestrant endocrine therapy, and mTOR inhibitor (exemestane+mTORi), respectively. As to subsequent therapy after fulvestrant, the response to chemotherapy was higher than that to endocrine therapy (**Table 5**).

The TTF of subsequent therapy with chemo+mTORi was significantly longer than that obtained with subsequent endocrine therapy after fulvestrant, i.e. 6.2 versus 2.8 months, respectively (HR=0.46; 95% CI, 0.293−0.728; P =0.0019) (**Fig. 3**).

Discussion

Fulvestrant is an option for treating hormone receptor positive, postmenopausal metastatic, and advanced breast cancer in patients and can be administered during any line of therapy. In this study, eligible patients were postmenopausal woman with locally advanced or metastatic ER-positive breast cancer who received treatment with fulvestrant. All patients were given endocrine therapies prior to fulvestrant administration. Fluvestrant was given as the third or later line of endocrine therapy to 70% of patients.

In our dataset, the median TTF for fulvestrant 500 mg was 6.1 months and median OS was 28.5 months.

In the CONFIRM study, which compared fulvestrant 500 mg to fulvestrant 250 mg for treatment of postmenopausal women with ER-positive advanced breast cancer who experienced progression after prior endocrine therapy, median progression free survival with fulvestrant 500 mg was 6.5 months[3] and median OS was 26.4 months[4]. The CONFIRM study included first and second-line fulvestrant therapy for hormone receptor positive advanced breast cancer. Our TTF data were nearly equivalent to those obtained in the CONFIRM study. Several cohort studies focusing on fulvestrant have been reported both in Japan and abroad[8,9]. In a cohort study

Table 5 Best overall response in patients with advanced or metastatic breast cancer who underwent post-fulvestrant therapy

	n	n, (%)						RR	CBR
		CR	PR	LSD	SD	PD	NE		
All	97	0	18	13	15	36	15	18.6	32
Endocrine therapy	42	0	1	4	7	21	9	2.4	12.2
Chemotherapy	54	0	17	8	8	15	6	31.2	46.3
ET+mTORi	1	0	0	1	0	0	0	0	100

CR, complete response; PR, partial response; LSD, long stable disease (>24 weeks SD), stable disease; PD, progressive disease; NE, not evaluable, RR, response rate=CR+PR, CBR, clinical benefit rate=CR+PR+LSD

Interruption of post-fulvestrant therapy due to any adverse events was 13.0% (7/54) with chemotherapy and 4.8% (2/42) with endocrine therapy.

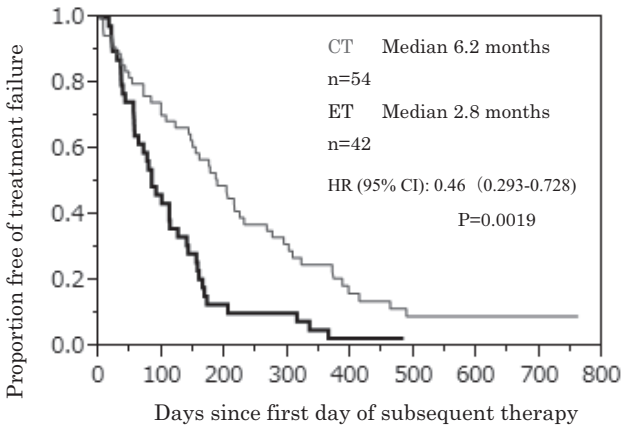

Fig. 3 Time to treatment failure for different subsequent-fulvestrant therapies
TTF, time to treatment failure; CT, chemotherapy; ET, endocrine therapy; HR, hazard ratio; CI, confidence interval

from Japan, 117 postmenopausal patients with metastatic or advanced cancer, who had received previous endocrine therapies, were treated with fulvestrant 500 mg. Median time to progression (TTP) for fulvestrant 500 mg was 6.1 months. This study also revealed the duration of first line endocrine therapy to have a significant association with TTP. In the retrospective trial conducted by Moscetti et al, 163 patients were treated with fulvestrant 500 mg. Median progression free survival was 7 months. According to these results and our present observations, the duration of efficacy for fulvestrant was almost half a year in the actual clinical setting. However, data from clinical trials may differ from those obtained in routine clinical settings. Actual experience with treatment agents and regimens may help physicians in their daily clinical practice.

As to subsequent therapy after fulvestrant, the response to chemotherapy was significantly higher than that to endocrine therapy. In this study, all patients received at least two endocrine therapies after fulvestrant. More than 70% of patients had previously received three endocrine therapies. Since hormone receptor sensitivity diminishes, endocrine therapy does not yield good responsiveness in the long term.

Molecularly-targeted therapies with mTORi are rarely used as subsequent therapy after fulvestrant. One of the reasons for this drug not being administered, might be that it had only been available for a short period when this study was being conducted. In a recent randomized controlled trial comparing the combination of the Cyclin Dependent Kinase (CDK) 4 and 6 inhibitor palbociclib and fulvestrant to fulvestrant with a placebo in patients who received at least one previous endocrine treatment with metastatic breast cancer, progression free survival was significantly longer in the former group than in that receiving the fulvestrant with a placebo[10]. However, in actual clinical settings, the cost of CDK 4/6 inhibitors is very high. To date, no data have been reported from clinical trials in which fulvestrant was administered first, for progressive cancer, versus treatment with a CDK 4/6 inhibitor added to fulvestrant. However, in cases in which the duration of previous endocrine therapy is long and there is no liver metastasis, it may be an option to start treatment with fulvestrant alone[8].

In conclusion, our study showed fulvestrant 500 mg to be an effective and well-tolerated treatment for postmenopausal women with metastatic breast cancer showing progression after endocrine therapies in actual clinical settings.

Conflict of Interest: None of the authors has any conflicts of interest to disclose.

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