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Fulvestrant ('Faslodex') in pre-treated patients with advanced breast cancer: A single-centre experience

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Abstract

Fulvestrant ('Faslodex') is a new oestrogen receptor (ER) antagonist with no agonist effects. This report describes the experience of a single centre including 126 postmenopausal women with advanced breast cancer (ABC) in a fulvestrant Compassionate Use Programme. All patients had previously received endocrine treatment for early or ABC. Patients received fulvestrant as first- ($n = 7$), second- ($n = 51$), third- ($n = 50$) or fourth-line endocrine therapy ($n = 18$) for ABC (median duration of treatment: 4 months [range 3–27^{+} months], follow-up: 13 months [range 1–38^{+} months]). Twelve patients had partial responses (PR) and 43 patients experienced stable disease (SD) $\geqslant$6 months (objective response rate: 9.5%; clinical benefit [CB] rate: 43.6%). Ten of 12 patients with a PR had HER2-negative tumours, and 9/12 had ER-positive and progesterone receptor (PgR)-positive disease (two patients had unknown HER2 status and one had unknown ER and PgR status). Nine of the 18 patients with HER2-positive tumours experienced CB with fulvestrant. Although CB rates were similar when fulvestrant was given as first- to fourth-line endocrine treatment, the proportion of those experiencing CB who had a PR appeared to decrease when fulvestrant was used later in the sequence. Fulvestrant was well tolerated; six patients experienced adverse events (all grade I/II). These data demonstrate that fulvestrant is an effective and well-tolerated therapy for patients with ABC progressing on prior therapies.

Keywords: Advanced breast cancer; Hormone receptor positive; Pre-treated; Fulvestrant; Clinical benefit

1. Introduction

Endocrine therapy is the preferred therapeutic choice in the treatment of recurrent or metastatic hormone receptor-positive breast cancer, since it produces disease control without the marked side effects associated with cytotoxic agents [1]. A response to one endocrine therapy has been recognised to be predictive of responses to further endocrine agents [2,3] and, as a result, the sequential use of these agents may prolong the time until the use of cytotoxic chemotherapy and is associated with significant quality-of-life (QoL) benefits. This is particularly relevant in patients with systemic, recurrent breast cancer for whom treatment will not be curative, but rather will aim to prolong survival and maintain or enhance QoL.

Fulvestrant ('Faslodex') is a new type of oestrogen receptor (ER) antagonist with no agonist effects [4]. Fulvestrant binds to the ER, preventing dimerisation and leads to accelerated degradation of the ER–fulvestrant complex and loss of functional oestrogen response [5]. In turn, the increased rate of ER

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degradation leads to a reduction in cellular levels of the progesterone receptor (PgR) [6]. The efficacy of fulvestrant has been compared with the aromatase inhibitor (AI) anastrozole in two phase III trials in postmenopausal women with hormone-sensitive breast cancer progressing on one prior endocrine therapy [7,8]. Fulvestrant was well tolerated in the studies and a prospectively planned combined analysis of the two trials demonstrated that fulvestrant was at least as effective as anastrozole, producing a median time to progression of 5.5 months *versus* 4.1 months (hazard ratio [HR] 0.95; 95.14% confidence intervals [CI] 0.82, 1.10; $P = 0.48$) and an objective response rate (OR) of 19.2% *versus* 16.5% (treatment difference 2.75%; 95.14% CI 2.27, 9.05; $P = 0.31$), respectively [9]. A combined analysis of overall survival for the trials was carried out when $\geqslant 75\%$ of patients had died and demonstrated that fulvestrant was not significantly different from anastrozole for time to death (TTD). Median TTD was 27.4 and 27.7 months for fulvestrant- and anastrozole-treated patients, respectively (HR 0.98; 95% CI 0.84, 1.15; $P = 0.81$) [10].

It is important to be aware of clinical experiences with fulvestrant in patients who have been treated with $\geqslant 1$ prior endocrine intervention to ensure that the clinical choices underpinning the sequential use of endocrine agents are fully informed. Fulvestrant's mechanism of action is distinct from other endocrine therapies and, therefore, this agent lacks cross-resistance with agents such as tamoxifen and the AIs. Further refinement of fulvestrant's placing in treatment schedules is important, since it will ensure that women derive optimal benefit from endocrine therapies.

Here we report on a single-centre experience from the University of Vienna. In a Compassionate Use Programme, women received fulvestrant for the treatment of advanced breast cancer after they had progressed on prior endocrine therapy.

2. Methods

All data were collected from the Division of Oncology at the University of Vienna, Vienna, Austria.

2.1. Patients

All patients were postmenopausal women with ER-positive and/or PgR-positive disease who had failed at least one prior endocrine therapy, either as adjuvant treatment or for the treatment of advanced disease. Menopausal status was assessed clinically (amenorrhoea > 1 year) and serologically (serum oestradiol within the postmenopausal range [<25 pg/ml] and serum follicle-stimulating hormone within the postmenopausal range [25.8–134.8 mU/ml]).

2.2. Treatment and assessments

Patients received fulvestrant 250 mg every 28 days by intramuscular injection, with treatment continuing until objective disease progression or other events that required discontinuation of treatment. After this point, treatment was stopped and further therapy was initiated at the discretion of the treating physician. Calculation of median disease-free interval from diagnosis until first relapse excluded all patients presenting with advanced disease ($n = 27$).

Response to treatment was assessed every 3 months using World Health Organisation (WHO) response criteria. As this was a single centre prescribing fulvestrant as part of a Compassionate Use Programme and not a controlled clinical trial, there was no external review of response rates. Responses were classified as complete response (CR), partial response (PR), stable disease (SD) $\geqslant 6$ months, or disease progression (PD). Patients experiencing SD >3 months but <6 months were also noted. CR was defined as the radiological disappearance of all measurable disease, PR was defined as a $\geqslant 50\%$ decrease in tumour size or in the sum of all measurable lesions and SD was defined as a <50% decrease or a <25% increase in tumour size without the appearance of new lesions. PD was defined as a >25% increase in tumour size or the appearance of new lesions. In patients with bone disease as the only metastatic site, response was evaluated by bone scintography, where SD was recorded if there was the same pattern of lesions that was of the same intensity as the previous scan and no new lesions were apparent. PR was recorded if the bone scan showed a marked decrease in the intensity of all lesions and there was additional evidence of recalcification of the lesion on magnetic resonance imagery scan.

Adverse events were recorded throughout the treatment period and were graded according to WHO toxicity criteria.

2.3. Hormone receptor and HER2 status

Hormone receptor status (ER and PgR) was assessed using immunohistochemistry, with tumour expression being classified as either positive (ER and/or PgR-positive) or negative (ER- and PgR-negative). Hormone receptor positivity was defined as in previous studies using an immunoreactive staining score constituting the proportion of positively staining cells and their staining intensity [11]. Tumour human epidermal growth factor receptor 2 (HER2) status was assessed using the Herceptest® (Dako A/S, Glostrup, Denmark) or dual colour fluorescent *in situ* hybridisation (FISH; PathVision® HER2 DNA probe kit, Vysis Inc., Downers Grove, IL, USA). Tumours were classed as HER2-positive if they

had a staining intensity of +++ on the Herceptest®; if a score of ++ was gained the tumours were reanalysed using FISH.

3. Results

3.1. Patient characteristics

A total of 126 patients are currently evaluable for efficacy and tolerability. The median age of the patients was 63 years (range 30–88 years) and all had invasive ductal or lobular adenocarcinoma at diagnosis. The median disease-free interval from diagnosis until first relapse was 3.8 years (range: 0.1–22.1 years). Bone and/or soft tissue metastases (with no visceral involvement) were present in 64 patients (50.8%), visceral metastases (with no bone/soft tissue involvement) were present in 17 patients (13.5%) and 45 patients (36.0%) had both bone/soft tissue and visceral metastases (Table 1). In more detail, metastases were present in the lungs in 37 patients (29.4%), in the liver in 33 patients (26.2%), in the bone in 87 patients (69.0%), in the lymph nodes in 29 patients (23.0%), in the soft tissue in 39 patients (30.9%), and in the bone marrow in two patients (1.6%). In addition, 20 patients (15.9%) had skin metastases and four patients (3.2%) had cerebral metastases.

Table 1
Patient and tumour characteristics at baseline

Characteristic	No. of patients (%)
Median age, years (range)	63 (30–88)
Median disease-free interval[a], years (range)	2.5 (0–22.1)
Sites of metastases	
Bone and/or soft tissue[b]	64 (50.8)
Visceral[c]	17 (13.5)
Both bone and/or soft tissue and visceral[d]	45 (36.0)
Hormone receptor status	
ER-positive and/or PgR-positive	115 (91.3)
ER-positive and PgR-positive	68 (54.0)
ER and PgR unknown	11 (8.7)
HER2 status	
Positive	18 (14.3)
Negative	91 (72.2)
Unknown	17 (13.5)
Prior adjuvant chemotherapy	54 (42.9)
Prior adjuvant endocrine therapy	75 (59.5)
Prior chemotherapy for advanced disease	75 (59.5)
Prior endocrine therapy for advanced disease	119 (94.4)

[a] From diagnosis to first relapse.
[b] Patients may have had additional sites of metastastases other than visceral disease.
[c] Patients may have had additional sites of metastastases other than bone or soft tissue disease.
[d] Patients may have had additional sites of metastastases.

3.2. Prior treatments

Adjuvant chemotherapy was received by 53 patients (42.1%) and 74 patients (59.2%) had previously been treated with chemotherapy for advanced disease. Most patients (75; 59.5%) had previously received adjuvant endocrine treatment and all but seven patients had previously received endocrine therapy for advanced disease (Table 2). The majority of these patients had received first-line therapy for advanced disease with either anastrozole or tamoxifen; other first-line treatments included exemestane, letrozole, formestane, goserelin, and also a combination of anastrozole and tamoxifen. Prior second-line treatments consisted mainly of exemestane or anastrozole. The only prior third-line endocrine therapy used was exemestane. A total of 108 patients (85.7%) had received prior non-steroidal AI (anastrozole or letrozole) treatment for advanced disease. Overall, of the 126 patients included in this analysis, fulvestrant was received by seven patients (5.5%) as first-line therapy, 51 patients (40.5%) as second-line therapy and 50 patients (39.7%) as third-line therapy for advanced breast cancer. Eighteen patients (14.3%) received fulvestrant as fourth-line therapy. Overall, the median time on prior endocrine therapy (for advanced disease) was 14 months (range: 0–96 months; 12 patients were excluded from the analysis because missing/incomplete data). The median duration of prior endocrine treatment increased as the line of fulvestrant therapy increased (second line: 8 months [range: 3–67 months];

Table 2
Endocrine therapies received for advanced breast cancer

	No. of patients (%)[a]
First-line therapies (n = 126)	
Tamoxifen	27 (21.4)
Anastrozole	73 (57.9)
Tamoxifen/anastrozole	3 (2.4)
Letrozole	8 (6.3)
Exemestane	6 (4.8)
Formestane	1 (0.8)
Goserelin	1 (0.8)
Fulvestrant	7 (5.5)
Second-line therapies (n = 120)	
Tamoxifen	9 (7.5)
Anastrozole	22 (18.3)
Letrozole	3 (2.5)
Exemestane	33 (27.5)
Medroxyprogesterone acetate	1 (0.8)
Fulvestrant	52 (43.3)
Third-line therapies (n = 67)	
Exemestane	18 (26.9)
Fulvestrant	49 (73.1)
Fourth-line therapies (n = 18)	
Fulvestrant	18 (100)

[a] Percentage presented as the proportion of the total number of patients receiving the appropriate line of treatment.

third line: 22 months [range: 5–84 months]; fourth line: 48 months [range: 14–96 months]). The median duration of fulvestrant treatment was 4 months (range 3–27^{+} months) and the median duration of follow-up was 13 months (range: 1–38^{+} months).

3.3. Efficacy

All 126 patients were evaluable for response. Overall, the median time to progression was 4 months (range 1–27^{+} months); in patients experiencing clinical benefit (CB; CR, PR or SD $\geqslant$ 6 months) prior to progression, the median time to progression was 6 months (range 6–27 months). Treatment with fulvestrant produced a PR in 12 patients and SD $\geqslant$ 6 months in 43 patients, leading to an OR rate of 9.5% and a CB rate of 43.6%. Fifteen patients (11.9%) experienced SD > 3 months but <6 months and 56 patients (44.4%) experienced *de novo* PD. Of the 108 patients who had previously received a non-steroidal AI for advanced disease, 47 (43.5%) gained CB with fulvestrant treatment.

Of the 12 patients who derived a PR with fulvestrant, two patients received fulvestrant as first-line, six as second-line and three as third-line treatment. One patient experienced a PR with fulvestrant as fourth-line therapy (Table 3). Interestingly, two patients with a PR had previously only experienced PD on prior endocrine treatments (tamoxifen and anastrozole [$n = 1$] and letrozole [$n = 1$], respectively) and only three of them had an objective response to prior treatment. Two of these 12 patients with PR to fulvestrant experienced a reduction in the size of visceral metastases (one patient receiving fulvestrant as second-line and one as fourth-line therapy), and 10 patients had a reduction in the size of bone metastases (two patients as first-line, five patients as second-line and three as third-line therapy). Seven patients who experienced a PR have now progressed; time to progression was 5 months ($n = 2$), and in individual patients, 6, 7, 8, 9, and 27 months. PRs are ongoing in five patients, with current durations of response being 6, 9 ($n = 2$), 12, and 27 months.

For patients experiencing SD $\geqslant$ 6 months, one patient received fulvestrant as first-line therapy, 17 patients received second-line fulvestrant, 19 patients received fulvestrant as a third-line treatment. Six patients attained SD $\geqslant$ 6 months with fulvestrant as fourth-line treatment. Eight of the patients experiencing SD $\geqslant$ 6 months have not yet progressed and are still receiving fulvestrant. The current duration of treatment in these patients ranges between 10 and 18 months. Thirty-three patients experienced SD $\geqslant$ 6 months but subsequently progressed; time to progression ranged between 6 and 24 months. All of the 15 patients who experienced SD > 3 and <6 months have now progressed.

In an analysis of response by line of fulvestrant treatment, similar CB rates were gained in patients receiving fulvestrant as first- to fourth-line endocrine treatment for advanced breast cancer (Fig. 1). Although numbers were small, the proportion of patients experiencing a PR appeared to decrease as fulvestrant was used later in the treatment sequence.

3.4. Hormone receptor and HER2 status

All but one of the patients experiencing a PR with fulvestrant were known to have ER-positive tumours (one had unknown ER/PgR status), with nine of 12 (75.0%) having both ER-positive and PgR-positive disease

Table 3
Status of fulvestrant therapy, sites of metastases and prior treatment responses in patients experiencing a partial response to fulvestrant

Patient	Fulvestrant (time to progression)	Sites of metastasis	Site of response	Prior endocrine therapies for advanced disease (responses)
1	First line (9 months)	Bone	Bone	None
2	First line (27^{+} months)[a]	Bone	Bone	None
3	Second line (9 months)	Liver, bone	Visceral	1. Anastrozole (SD)
4	Second line (5 months)	Lung, bone, soft tissues	Bone	1. Anastrozole (PR)
5	Second line (8 months)	Lung, bone, soft tissues	Bone	1. Tamoxifen (SD)
6	Second line (7 months)	Bone, skin, soft tissues	Bone	1. Anastrozole (SD)
7	Second line (9^{+} months)[a]	Lung, bone, skin	Bone	1. Anastrozole (PR)
8	Second line (6^{+} months)[a]	Bone	Bone	1. Letrozole (PD)
9	Third line (6 months)	Bone	Bone	1. Tamoxifen (PD) 2. Anastrozole (PD)
10	Third line (5 months)	Lung, bone, skin	Bone	1. Tamoxifen (SD) 2. Exemestane (SD)
11	Third line (12^{+} months)[a]	Liver, soft tissues	Bone	1. Anastrozole (PR) 2. Exemestane (PD)
12	Fourth line (27 months)	Lung, bone	Visceral	1. Tamoxifen (SD) 2. Anastrozole (SD) 3. Exemestane (PD)

PR, partial response; SD, stable disease; PD, disease progression.
[a] Current duration of treatment ongoing, not yet progressed.

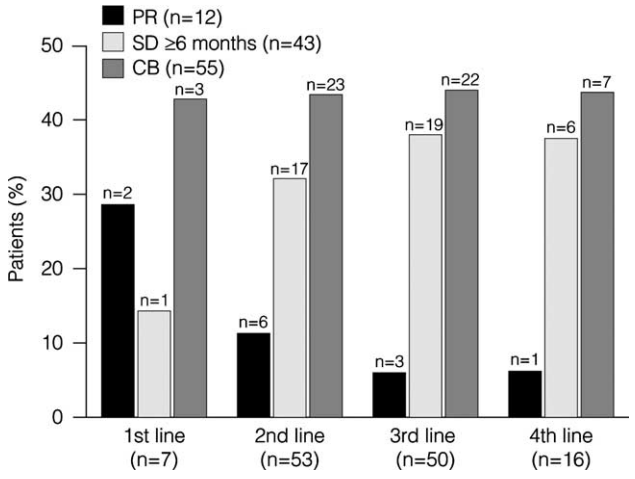

Fig. 1. Objective response and clinical benefit rate by line of fulvestrant treatment. Denominator in each case was the total number of patients receiving first, second, third and fourth line fulvestrant, respectively.

(Table 4). Twenty-six of the 43 patients (60.5%) deriving SD $\geqslant$ 6 months with fulvestrant also had ER-positive and PgR-positive disease, with 12 patients (27.9%) in this group having ER-positive and PgR-negative tumours. ER-negative/PgR-positive disease was found in only three patients, two of whom experienced PD on fulvestrant and one had SD $\geqslant$ 6 months. HER2 status was known in 109/126 patients (86.5%). Seventy-nine patients (62.7%) were known to have HER2-negative disease, with only 30 patients (23.8%) known to have tumours that were HER2-positive (Table 4). Of the patients with HER2-positive disease, nine experienced PD and nine experienced SD $\geqslant$ 6 months.

3.5. Tolerability

In this group of patients, many of whom had been heavily pre-treated, fulvestrant was well tolerated and no WHO grade III/IV toxicities were observed. Grade I/II adverse events were experienced by six patients (4.8%), and these were grade I nausea ($n = 1$), grade II nausea/non-specific abdominal pain ($n = 1$), grade I weight gain ($n = 2$), grade II headache ($n = 1$) and grade I hot flushes ($n = 1$). No patients experienced pain or other reaction at the injection site.

4. Discussion

The results presented here demonstrate that fulvestrant 250 mg is an effective and well-tolerated treatment for women with advanced breast cancer who have progressed on prior endocrine therapies. Fulvestrant produced a CB rate of 43.6% and an OR rate of 9.5%, confirming previous studies that have shown fulvestrant to be an effective treatment option in pre-treated women with advanced breast cancer [12–14]. Ten of the 12 patients with a PR had a response in bone with the remaining two having a reduction in the size of visceral metastases. These data also reinforce the results of two phase III studies where fulvestrant was shown to be effective in patients who had progressed on tamoxifen [7,8]. Similar CB rates were observed independent of when fulvestrant was given in the endocrine treatment sequence. However, the likelihood of experiencing an OR appeared to decrease when fulvestrant was used later in the treatment sequence, although numbers were small and so these data must be interpreted with caution.

These data demonstrate that fulvestrant's novel mechanism of action results in a lack of cross-resistance with other endocrine therapies. The majority of patients had received prior treatment with an AI (predominantly first- and second-line anastrozole, and third-line exemestane) and many had also received tamoxifen as first-line treatment for advanced disease. Results from an ongoing phase II study have shown that fulvestrant produced CB in 19/67 (28%) patients who had progressed on prior treatment with tamoxifen and an AI [12]. Results from the present study support the conjecture that fulvestrant may be effective following AI failure, with 43% of the 108 patients who had

Table 4
Patients' hormone receptor status and HER2 status by response to fulvestrant treatment

	Response to fulvestrant			
	PR ($n = 12$)	SD $\geqslant$ 6 months ($n = 43$)	SD $\geqslant$ 3 but <6 months ($n = 15$)	PD ($n = 56$)
Hormone receptor status				
ER positive/PgR positive	9	26	3	30
ER positive/PgR negative	2	12	8	22
ER negative/PgR positive	0	1	0	2
Unknown	1	4	4	2
HER2 status				
Positive	0	9	0	9
Negative	10	26	12	43
Unknown	2	8	3	4

SD, stable disease; PR, partial response; PD, disease progression.

previously received a non-steroidal AI (in the advanced disease setting) gaining CB with fulvestrant treatment.

Importantly, treatment with fulvestrant does not preclude further endocrine therapy. In a retrospective analysis of the two phase III trials, 25/54 patients who derived CB on second-line fulvestrant achieved a PR or SD $\geqslant$ 6 months on subsequent treatment with anastrozole, letrozole or megestrol acetate [15]. In a further phase III study in which fulvestrant was used as a first-line treatment, 20/35 patients experiencing CB with fulvestrant derived CB from subsequent endocrine therapy with agents such as tamoxifen, anastrozole and megestrol acetate [16]. These results demonstrate that fulvestrant may be used early in the endocrine sequence without having a detrimental effect on responses to subsequent treatments. Importantly, these data also emphasise the sequence versatility of fulvestrant, which will allow treatment sequences to be tailored to the individual patient.

Receptor status was examined as part of our study, and most of the patients (89%) were confirmed as having ER-positive disease. A slightly higher proportion of patients was confirmed to have PgR-positive disease (56%) compared with PgR-negative (35%). Hormone receptor status was unknown in 9% of patients. In the patients deriving a PR from fulvestrant, 9/12 patients had tumours that were both ER-positive and PgR-positive, suggesting that these patients may gain particular benefit from fulvestrant treatment. Recently, an exploratory analysis of treatment response by hormone receptor status has been performed in a study of fulvestrant in the first-line treatment of advanced breast cancer. In that study patients with tumours expressing both ER and PgR appeared to respond better to fulvestrant compared with patients with tumours expressing ER and/or PgR. The median time to progressions of 11.4 and 8.2 months observed for each subgroup, respectively. Furthermore, fulvestrant-treated patients with both ER-positive and PgR-positive disease appeared to experience a higher objective response rate compared with those with ER-positive and/or PgR-positive disease (44.3% *versus* 33.2%, respectively) [17,18]. In our study, the majority of patients were HER2-negative, and 10 of the patients attaining a PR were HER2-negative (two patients had unknown HER2 status), as may be predicted from the association of HER2-positive disease with endocrine-resistance [19]. Notably, however, nine of the 18 patients known to have HER2-positive disease did gain CB from fulvestrant treatment. This is in line with preclinical data suggesting that fulvestrant may be effective in HER2-positive tumours [20].

Fulvestrant treatment was associated with no grade III/IV toxicity, and only a very limited number of grade I/II adverse events. These data confirm previous studies that have shown fulvestrant to be very well tolerated. Fulvestrant is associated with a lower incidence of joint disorders compared with anastrozole [9], and with a lower incidence of hot flushes compared with tamoxifen [18].

In summary, fulvestrant has been shown to be active and well tolerated in patients who had been pre-treated with prior endocrine therapies. The novel mechanism of action of fulvestrant limits the potential for cross-resistance with other commonly used endocrine agents, such as the AIs and tamoxifen. It is important that new therapies such as fulvestrant are incorporated into rationally designed endocrine sequences for treating patients with newly diagnosed advanced disease. Experience from the Compassionate Use Programme may suggest that the early incorporation of fulvestrant into the treatment sequence allows patients to derive maximum benefit from this new, effective and well-tolerated endocrine therapy. However, the optimum sequence of endocrine therapies is yet to be defined and is under continual evaluation [21]. Data from two phase III studies has demonstrated fulvestrant to be at least as effective as the third-generation AI anastrozole following progression on/after antioestrogen therapy and evidence is accumulating to support its use following progression on/after AIs. Ongoing phase III studies are further evaluating the efficacy of fulvestrant after non-steroidal AI failure and also are looking at this agent in various combination treatment regimens (e.g. with anastrozole, gefitinib and trastuzumab). Such trials will further define the optimum position of fulvestrant in the endocrine treatment sequence for postmenopausal women with advanced breast cancer.

Conflicts of interest statement

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