Fulvestrant for the Treatment of Advanced Breast Cancer in Postmenopausal Women: A Japanese Study

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Abstract. Background: Fulvestrant (‘Faslodex’) is a new type of oestrogen receptor (ER) antagonist that down-regulates the ER and has no known agonist effects. Patients and Methods: In this open-label, Phase II trial, 30 postmenopausal Japanese women with hormone-sensitive advanced breast cancer, who had progressed on tamoxifen/toremifene following an initial response, received fulvestrant (250 mg; once-monthly intramuscular injection). Primary endpoints were objective tumour response rate (complete or partial response) and assessment of tolerability; secondary endpoints included clinical benefit (objective response, or stable disease ≥ 24 weeks), duration of response and pharmacokinetic analysis. Results: The objective response rate was 23.3% and 60.0% of patients experienced clinical benefit. Adverse events were generally mild; the most common were pharyngitis (26.7%), headache (23.3%) and nausea (20.0%). Pharmacokinetic data were similar to a Western study of postmenopausal patients. Conclusion: Fulvestrant 250 mg/month is effective and well-tolerated in Japanese patients who have relapsed after one prior endocrine treatment.

Fulvestrant (‘Faslodex’) is a new type of antioestrogen, an oestrogen receptor (ER) antagonist that down-regulates the ER. Binding of fulvestrant to the ER reduces ER dimerisation and leads to rapid degradation and loss of ER protein, with a subsequent reduction in ER-dependent progesterone receptor (PgR) expression. Fulvestrant blocks the trophic effects of oestrogen but, unlike tamoxifen, has no known agonist effects (1-5). The partial agonist effects of tamoxifen are associated with a slightly increased risk of endometrial cancer and stimulation of recurrent disease (6). Despite the development of third-generation, non-steroidal aromatase inhibitors (AIs), such as anastrozole and letrozole, which provide an alternative hormonal approach, there remains a need for additional effective and well-tolerated therapeutic agents for the sequential treatment of advanced breast cancer (2).

Fulvestrant demonstrated clear efficacy in a Phase II trial in postmenopausal women with advanced breast cancer resistant to tamoxifen (7-9). Following on from these encouraging results were two large, multicentre, randomised Phase III trials (trial 0020 performed in Europe, Australia and South Africa; trial 0021 performed in North America) which compared fulvestrant (250 mg once monthly, via intramuscular [i.m.] injection) with anastrozole (1 mg once daily, orally). These trials recruited postmenopausal women with hormone-sensitive advanced breast cancer that had progressed on prior endocrine therapy (mostly tamoxifen) (10, 11). The primary endpoint of both trials was time to progression and, for this endpoint, median values for fulvestrant vs anastrozole were 5.5 vs 5.1 months (hazard ratio [HR]: 0.98; 95.14% confidence intervals [CI] 0.80, 1.21; p=0.84) in trial 0020 and 5.4 vs 3.4 months (HR: 0.92, 95.14% CI 0.74, 1.14; p=0.43) in trial 0021. In both trials no significant difference in efficacy was detected between the two agents, leading to the conclusion that fulvestrant is at least as effective as anastrozole in this setting. Both fulvestrant and anastrozole were well-tolerated; the only significant difference in tolerability was a lower incidence of joint disorders...
(arthralgia) in the fulvestrant-treated group, arthralgia being an effect common to the non-steroidal AIs.

The present study was conducted to investigate the efficacy, safety and pharmacokinetics of fulvestrant in postmenopausal Japanese women with relapsed or advanced breast cancer who had progressed on tamoxifen/toremifene following an initial response.

Patients and Methods

Trial design. This was a Japanese open-label, Phase II study conducted at 13 centres. The primary objectives of this trial were to investigate the efficacy and safety of fulvestrant in postmenopausal women with hormone-sensitive advanced breast cancer who had relapsed or progressed after initially responding to tamoxifen or toremifene therapy. The secondary objective was to determine the pharmacokinetic profile of fulvestrant after repeated administration. The study was conducted in accordance with good clinical practice and the Declaration of Helsinki, and all eligible patients had to provide written informed consent.

Inclusion criteria. The patient population comprised postmenopausal women with histologically or cytologically confirmed hormone-sensitive breast cancer who had progressed on tamoxifen/toremifene following an initial response. Response to prior treatment for advanced disease was defined as a complete response (CR), partial response (PR), or stable disease (SD) ≥ 24 weeks. In addition, patients were also eligible if they had responded to adjuvant tamoxifen or toremifene after surgery, providing they remained disease-free for at least 2 years during therapy, prior to relapse. Women were considered postmenopausal if they fulfilled any one of the following criteria: ≥ 60 years of age; ≥ 45 years of age with amenorrhoea and no hysterectomy; follicle-stimulating hormone levels within postmenopausal range; or having undergone a bilateral oophorectomy. In addition, patients were required to have at least one measurable or evaluable (nonmeasurable) lesion for inclusion in the trial.

Exclusion criteria. Patients were excluded from the trial if they had a World Health Organisation (WHO) performance status of 3 or 4, or life expectancy < 3 months from the start of the study. Additional exclusion criteria included: life-threatening metastatic visceral disease (defined as extensive hepatic involvement, any degree of brain or leptomeningeal involvement, or symptomatic pulmonary lymphangitic spread); platelet count <100 x 10⁹/L; total bilirubin >1.5 times the upper limit of the reference range (ULRR); alanine aminotransferase or aspartate aminotransferase >2.5 times the ULRR in the absence of any liver metastases, or >5 times the ULRR if liver metastases were present; any evidence of severe or uncontrolled systemic disease or concomitant condition that would make it undesirable for the patient to participate in the study; systemic chemotherapy or radiotherapy within the previous 4 weeks; any prior treatment with fulvestrant or other endocrine therapies (except tamoxifen or toremifene); history of systemic malignancy within the previous 3 years (other than breast cancer and adequately treated in situ carcinoma of the cervix, uterus, or basal or squamous carcinoma of the skin); history of luteinising hormone-releasing hormone (LHRH) analogue treatment for breast cancer, or, if not given for breast cancer, treatment within 3 months (or 4 months in the case of depot formulation); treatment with a non-approved or investigational drug within 12 weeks; history of bleeding diathesis or long-term anticoagulant therapy (other than antiplatelet therapy).

Treatment. Fulvestrant (250 mg) was administered slowly as a single 5-ml i.m. injection into the buttock. This was given once monthly, defined as every 28 (± 3) days, during the 6-month study treatment period. Treatment continued until withdrawal due to disease progression, an unacceptable adverse event (AE), non-compliance, withdrawal of consent, or until the 6-month study treatment period was complete. At 6 months, responding patients continued treatment on a compassionate use programme.

Efficacy. Objective tumour assessments were performed at screening (within 4 weeks before registration) and were repeated every 12 weeks during the study treatment period. Skin or soft tissue lesions were also clinically assessed by physical examination every 4 weeks for the first 12 weeks. Tumour response was assessed as CR, PR, SD ≥ 24 weeks or disease progression (PD) in accordance with the Union Internationale Contre Le Cancer (UICC) criteria.

The primary efficacy endpoint of this trial was the objective tumour response rate, which was defined as the proportion of patients with a best overall tumour assessment of CR or PR. Secondary efficacy endpoints included clinical benefit rate (proportion of patients with an objective tumour response or SD ≥ 24 weeks), duration of response, duration of clinical benefit, time to progression and time to response. The duration of response was calculated (in patients with CR or PR) as the time from the first day of study treatment until disease progression was first observed. The same criteria were used to calculate the duration of clinical benefit (in patients with CR or PR or SD ≥ 24 weeks). Objective response and clinical benefit rates were also calculated by subpopulation, with patients stratified according to: prior tamoxifen or toremifene treatment for advanced disease or as adjuvant therapy, hormone receptor status, or site of lesion.

Statistical analysis of efficacy endpoints was performed for patients who fulfilled all entry requirements of the trial and who received study treatment at least once. All endpoints were calculated with 95% CIs and those involving median times or durations were calculated using the Kaplan-Meier method.

Safety. Adverse events (AEs) were defined as any deterioration in a patient’s condition that was not unequivocally due to disease progression. These were monitored during study treatment and the 8-week follow-up period following the last i.m. injection. AEs were grouped according to the FDA Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) classification and were classified as mild, moderate or severe in intensity. Patients were also monitored for clinical and laboratory toxicity throughout the treatment period.

Pharmacokinetics. Blood samples for plasma concentration assessment were collected every 4 weeks for the first 24 weeks, up to the sixth administration of fulvestrant. These samples were collected immediately before injection of fulvestrant in order to determine the minimum plasma concentrations after repeated administration and the data was used to estimate the time to reach
steady-state levels. The geometric mean (Gmean), Gmean±standard deviation, coefficient of variation (CV), minimum and maximum were calculated for the minimum plasma concentration data at each assessment.

Results

Patient demography. A total of 30 Japanese patients of median age 61.0 years (range 44 to 82 years) were enrolled in this study; demographic data are summarised in Table I. Seventeen patients (56.7%) had previously received tamoxifen or toremifene therapy for advanced disease and initially responded but then had confirmed progression. The remaining 13 patients (43.3%) had been disease-free for at least 2 years while receiving tamoxifen or toremifene as adjuvant treatment, but had either relapsed during therapy or within 12 months after adjuvant therapy.

Primary endpoints. Of the 30 patients included in this study, there were no patients with a CR, while seven patients experienced a PR, producing an objective response rate of 23.3% (95% CI 9.9, 42.3). The efficacy results are summarised in Table II.

Secondary endpoints. In addition to the observed objective responses, 11 patients had SD ≥ 24 weeks (Table II). Therefore, the proportion of patients with clinical benefit (CR + PR + SD ≥24 weeks) was 60.0% (95% CI 40.6, 77.3). Analysis of objective response rate within patient subpopulations showed that there was no difference in response rate or clinical benefit rate in patients stratified according to previous breast cancer treatment or hormone receptor status (Table III). In patients with lesions in soft tissues (breast, skin/soft tissue, or lymph nodes) only the response rate was 33.3%, while in patients with lesions in bone only or bone and soft tissue only, the response rate was 11.1%.

The median duration of response was 8.3 months (95% CI 6.3, 11.7) and the mean duration of clinical benefit was 9.8 months (95% CI 8.7, 10.8); both ranged from 5.6 to 13.0 months or longer (fewer than 50% of patients had disease progression, therefore the median duration of clinical benefit was not calculable by the Kaplan-Meier method) (Figure 1). The median time to progression, calculated for all treated patients, was 8.3 months (95% CI 6.4, 8.8), ranging from 1.9 to 13.0 months (Figure 2). Time to response ranged from 1.0 to 5.9 months, the median being 2.8 months, (95% CI 1.8, 5.5).
Fulvestrant was administered to all 30 patients who enrolled in the study, with patients receiving 8.5 i.m. injections on average. The median duration of treatment was 8.3 months, ranging from 2.8 to 12.9 months.

The most common AEs included pharyngitis (eight patients, 26.7%), headache (seven patients, 23.3%), nausea (six patients, 20.0%) and vomiting (five patients, 16.7%). AEs were observed in 28 of the 30 patients treated with fulvestrant; the majority of patients (24 patients) only experienced mild AEs, three patients experienced moderate AEs and one patient experienced a severe AE (pathological fracture).

Nineteen of the 30 patients (63.3%) experienced drug-related AEs but with one exception, these events were all mild (Table IV). Injection-site pain (four patients, 13.3%) and hyperglycaemia (three patients, 10.0%) were the only drug-related AEs reported by three (10.0%) or more patients. Other AEs relating to the site of i.m. injection were injection-site reaction and inflammation, each reported once by only one patient (3.3%), and all of the AEs relating to the injection site were of mild intensity. During the study a total of 255 injections were administered, of which seven (2.7%) resulted in an injection-site reaction. Drug-related AEs of the digestive system included diarrhoea, nausea, vomiting and abnormal liver function, being each observed in one patient (3.3%). Similarly, a drug-related AE of hot flushes (vasodilation) was seen in only one patient (3.3%).

Only one patient experienced a severe AE, a pathological fracture of lumbar vertebrae due to osteoporosis. This patient had osteoporosis before the study began and had also previously experienced a fracture of thoracic vertebrae. The possibility that the lumbar vertebrae fracture was due to the study treatment was low. However, as this possibility could not be completely excluded by the investigator, the AE was classified as drug-related.

Of the 30 patients who received fulvestrant, 18 (60.0%) were withdrawn due to objective disease progression while 12 (40%) completed the 6-month study treatment period. No patients were withdrawn due to AEs.

### Table III. Objective response and clinical benefit rates by subpopulation.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>n</th>
<th>Objective response (%)</th>
<th>Clinical benefit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>5 (29.4)</td>
<td>10 (58.8)</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>2 (15.4)</td>
<td>8 (61.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormone receptor status</th>
<th>n</th>
<th>Objective response (%)</th>
<th>Clinical benefit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+ or PgR+</td>
<td>28</td>
<td>6 (21.4)</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>ER+ and PgR+</td>
<td>21</td>
<td>4 (19.0)</td>
<td>14 (66.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sites of lesion</th>
<th>n</th>
<th>Objective response (%)</th>
<th>Clinical benefit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue only</td>
<td>62</td>
<td>(33.3)</td>
<td>3 (50.0)</td>
</tr>
<tr>
<td>Bone only or bone and soft tissue only</td>
<td>9</td>
<td>1 (11.1)</td>
<td>5 (55.6)</td>
</tr>
<tr>
<td>Visceral involvement (lung or liver)</td>
<td>15</td>
<td>4 (26.7)</td>
<td>10 (66.7)</td>
</tr>
</tbody>
</table>

**Table IV. Drug-related adverse events observed in > 5% of patients.**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Urogenital system</td>
<td></td>
</tr>
<tr>
<td>Leukorrhoea</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Vaginal haemorrhage</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Hypophosphataemia</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Lactate dehydrogenase increased</td>
<td>2 (6.7)</td>
</tr>
</tbody>
</table>

*All drug-related adverse events in >5% of patients were reported as mild (observed from initial administration up to end of follow-up period [8 weeks after last injection]).

Safety. Fulvestrant was administered to all 30 patients who enrolled in the study, with patients receiving 8.5 i.m. injections on average. The median duration of treatment was 8.3 months, ranging from 2.8 to 12.9 months.

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Of the 30 patients who received fulvestrant, 18 (60.0%) were withdrawn due to objective disease progression while 12 (40%) completed the 6-month study treatment period. No patients were withdrawn due to AEs.
Pharmacokinetics. Gmean minimum plasma concentrations increased steadily from 3.55 ng/ml at 4 weeks after the first dose to 6.80 ng/ml at 4 weeks after the fifth dose (Figure 3). At the final measurement, 4 weeks after the sixth dose, the Gmean minimum plasma concentration was 6.95 ng/ml and it was estimated that steady-state levels were reached at 4 weeks after the fifth or sixth dose. The accumulation ratio was approximately 2.0.

Discussion

Fulvestrant is currently approved in the USA and Brazil for the treatment of postmenopausal women with ER-positive metastatic breast cancer who have disease progression following prior antiestrogen therapy. Two large Phase III trials showed that fulvestrant is at least as effective as anastrozole in treating postmenopausal women with advanced breast cancer resistant to prior antiestrogen therapy (10, 11).

This trial assessed the efficacy, safety and pharmacokinetics of fulvestrant (250 mg) in 30 postmenopausal Japanese women with advanced breast cancer who had previously received and responded to tamoxifen or toremifene therapy. Fulvestrant demonstrated anti-tumour activity, with an objective response rate of 23.3% and a clinical benefit rate of 60.0%. These data are in line with previous Phase III trials, in which fulvestrant demonstrated objective response rates of 17.5–20.7% and clinical benefit rates of 42.2–44.6% (10, 11). Twelve patients who received clinical benefit with fulvestrant continued to receive treatment on a compassionate use basis after the completion of the trial. Treatment is still ongoing for four of these patients, who have all now received fulvestrant for longer than 3 years without PD.

Fulvestrant was well-tolerated in this population, with no patients withdrawing due to AEs and the majority of patients only experiencing mild AEs. The only drug-related AEs reported by three (10.0%) or more patients were injection-site pain (four patients, 13.3%) and hyperglycaemia (three patients, 10.0%).

Pharmacokinetic results were consistent with those from a Western study (11, 12), in which steady-state levels were reached at 4 weeks after the sixth dose, the accumulation ratio was approximately 2.3 and the Gmean minimum plasma concentration-time profile was similar (Figure 3). Therefore, based on the results of this trial, ethnicity does not appear to affect the pharmacokinetics of fulvestrant.

Fulvestrant is an effective and well-tolerated treatment for Japanese postmenopausal women with relapsed or advanced breast cancer who have initially responded to, but later progressed on, prior tamoxifen or toremifene therapy.

Appendix

Study Institutions: Niigata Cancer Centre Hospital, Niigata; National Cancer Centre Hospital, Tokyo; St Luke’s International Hospital, Tokyo; Saitama Cancer Centre Hospital, Saitama; Aichi Cancer Centre, Aichi; Nagoya City University Medical School, Aichi; Osaka Medical Centre for Cancer and Cardiovascular Diseases, Osaka; Osaka University Medical School, Osaka; Osaka National Hospital, Osaka; National Shikoku Cancer Centre Hospital, Ehime; National Kyushu Cancer Centre, Fukuoka; KitaKyushu Municipal Medical Centre, Fukuoka; Kumamoto City Hospital, Kumamoto, Japan.
References


