Examination of the Efficacy of Fulvestrant 500 mg Targeting Estrogen Receptor-Positive Postmenopausal Metastatic Breast Cancer: Prospective Observational Study (PerSeUS BC03 Study)

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Abstract

This multi-institutional prospective cohort study aimed to examine the efficacy and safety of 500 mg of Fulvestrant (Ful-500) in postmenopausal Estrogen Receptor (ER)-positive Advanced or Recurrent Metastatic Breast Cancer (AMBC). Patients with second, third or fourth-line Endocrine Therapy (ET) were recruited. From August 2013 to June 2016, participants were administered Ful-500 as two 5-mL intramuscular injections on days 0, 14, and 28 and thereafter, every 28 days until disease progression. The primary endpoint was Progression-Free Survival (PFS). Overall Response Rate (ORR), Clinical Benefit Rate (CBR), and safety were the secondary endpoints. For PFS, the Kaplan-Meier method was used to estimate the survival curve with a threshold Median Survival Time (MST) of 3 months and an expected MST of 5.5 months, at a one-sided significance level of 0.05 and power of 0.8. All statistical tests were two-sided. A 5% error was used in the PFS analysis. Of the 51 enrolled patients, 46 (second-line: 31, third-line: 10, fourth-line: 5) were analyzed. The median PFS duration was 8.5 months (95% confidence interval [CI], [5.6-14.5]). Furthermore, the 90% CI of the mean PFS was 5.6-14.5 months. The lower 90% CI value was higher than the median PFS (3 months) threshold, signifying that Ful-500 use was effective in these patients. The ORR and CBR values were 6.5% (3/46) and 71.7% (33/46), respectively. Adverse events, all grades 1-2, were observed in 15 cases (32.6%). Ful-500 use was effective and safe in second to fourth-line ET for ER-positive postmenopausal AMBC.

Introduction

Breast cancer is the most commonly diagnosed cancer among women and the leading cause of cancer-related death, worldwide [1]. More than two-thirds of breast cancer patients have the Estrogen Receptor (ER)-positive form of the disease [2,3]. The main treatment aims for Advanced or Metastatic Breast Cancer (AMBC) are survival prolongation and Quality of Life (QOL) improvement. For postmenopausal women with ER-positive locally AMBC, Endocrine Therapy (ET) is recommended, particularly in cases with non-life-threatening situations as seen in the Hortobagyi algorithm [4]. As first-line drugs, third-generation aromatase inhibitors (AIs; Anastrozole, Letrozole, or Exemestane) are widely used due to their safety and clinical superiority to tamoxifen in terms of the time to progression [5-8]. However, another agent Fulvestrant with a different mechanism of action, has been developed, which is a selective ER degrader, that blocks ER function by inducing its degradation [9,10]. In second-line ET, 250 mg of Fulvestrant (Ful-
250 has been shown to yield a Progression-Free Survival (PFS) rate which is similar to that observed for several AIs [11-14]. In particular, recent clinical trials have demonstrated that the administration of 500 mg of Fulvestrant (Ful-500) is more effective than Ful-250 for postmenopausal hormone receptor-positive Metastatic Breast Cancer (MBC) patients [15,16]. Fulvestrant, administered in three dose regimens (approved dose, loading dose, and high dose) and used in second-line ET, has demonstrated similar efficacy and tolerability in both Japanese and western populations, with analyses determining the optimal dose at 500 mg of Fulvestrant [17,18].

In Japan, Fulvestrant has been used for postmenopausal MBC patients since its approval in 2011. In fact, it has been widely used for ER-positive AMBC patients in second-line therapy and higher. A large-scale retrospective cohort study was conducted to investigate the current status of Fulvestrant use in Japan [19]. While that study seems to reflect the real-world status of Fulvestrant use in Japan, there is a lack of prospective data concerning the efficacy and safety of Fulvestrant in the country. In the FALCON study, the use of Ful-500 as a first-line drug for MBC led to a PFS duration greater than 16 months [20,21], indicating that monotherapy with Ful-500 may be useful in ER-positive AMBC. However, few reports have focused on the efficacy of Ful-500 in clinical practice. Accordingly, we performed a prospective cohort study focusing on the efficacy and safety of Ful-500 monotherapy as part of second to fourth-line ET for ER-positive postmenopausal AMBC patients.

**Materials and Methods**

The PerSeUS BC03 study (UMIN000011976) is a multicenter, phase II, prospective cohort study. The primary endpoint of the study was the evaluation of the PFS in patients treated with Ful-500, and the secondary endpoints were Objective Response Rate (ORR), Clinical Benefit Rate (CBR), and safety.

**Patients**

Eligible patients included postmenopausal women with MBC who had demonstrated ER-positive in the primary or metastatic tumor tissue (≥ 1% positive staining by immunohistochemistry on local laboratory testing) [22]. In addition, patients were required to have second, third, or fourth-line ET. Second-line endocrine therapy was to have relapsed during, or within 12 months after the completion of, adjuvant endocrine therapy; be in progression while on ET that was started more than 12 months after prior adjuvant endocrine therapy; or be in progression while on ET administered for de novo advanced disease. The provision of any form of chemotherapy for AMBC was not allowed. Patients had to have a performance status between 0 and 2. Those with uncontrolled life-threatening metastatic diseases such as severe liver metastasis, brain metastasis, carcinomatous lymphangitis and inflammatory breast cancer, allergies to Fulvestrant, and a history of previous Fulvestrant use were excluded. All patients provided written informed consent for participation. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee or review board of each participating institution.

**Table 1: Summary of patient’s characteristic.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Efficacy analysis sets n=46 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median Range</td>
<td>69 [45-82]</td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37 (80.4)</td>
</tr>
<tr>
<td>1</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>Metastatic pattern</td>
<td></td>
</tr>
<tr>
<td>Recurrent de novo metastatic</td>
<td>35 (76.1)</td>
</tr>
<tr>
<td>Treatment lines</td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>31 (67.4)</td>
</tr>
<tr>
<td>Third</td>
<td>10 (20.4)</td>
</tr>
<tr>
<td>Fourth</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>MBC diagnosis to F500 use (years)</td>
<td>1.8</td>
</tr>
<tr>
<td>Median Range</td>
<td>[0.0-13.4]</td>
</tr>
<tr>
<td>Hormonal receptor</td>
<td></td>
</tr>
<tr>
<td>ER(+) PgR(+)</td>
<td>34 (73.9)</td>
</tr>
<tr>
<td>ER(+) PgR(-)</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>ER(+) PgR(NA)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>HER2</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>39 (84.9%)</td>
</tr>
<tr>
<td>Positive</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Missing</td>
<td>5 (10.8%)</td>
</tr>
<tr>
<td>Visceral metastasis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (41.3)</td>
</tr>
<tr>
<td>No</td>
<td>27 (58.7)</td>
</tr>
<tr>
<td>Central nerve metastasis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>No</td>
<td>49 (100.0)</td>
</tr>
<tr>
<td>Period from diagnosis to Fulvestrant use (months)</td>
<td>8</td>
</tr>
<tr>
<td>Second</td>
<td>8</td>
</tr>
<tr>
<td>Third</td>
<td>25</td>
</tr>
<tr>
<td>Fourth</td>
<td>49</td>
</tr>
</tbody>
</table>

*Abbreviation: MBC: Metastatic Breast Cancer; ER: Estrogen Receptor; PgR: Progesterone Receptor*

**Study treatment**

From August 2013 to June 2016, eligible patients were administered Ful-500 (high dose) as two 5-mL intramuscular injections on days 0, 14, and 28, and then every 28 days thereafter. Treatment with Ful-500 was continued until disease progression or until any other discontinuation criterion was met.

**Study assessments**

The primary endpoint was PFS. CBR, ORR, and safety were the secondary endpoints. Efficacy was assessed using PFS, ORR (defined by Complete Response [CR] and Partial Response [PR]) and CBR (defined by complete response, partial response and Stable Disease [SD] lasting longer than 24 weeks). Generally, in clinical trials, measurable metastatic sites such as the lung, liver and lymph node are required, whereas most bone metastases are non-measurable. Measurable lesions were estimated by CT or MRI (≤ 5-mm slice). All patients were followed-up every 12 weeks for progression. In this study, based on RECIST criteria, the unequivocal progression of non-CR/non-Progressive Disease (PD) lesions was evaluated by a combination of several modalities (e.g. CT, MRI, PET/CT and bone scintigraphy [24]), tumor marker levels, and worsening symptoms. Patients with non-measurable lesions diagnosed as non-CR/non-PD were classified as having SD [23].

Safety was evaluated by the assessment of Adverse Events (AEs) classified according to the National Cancer Institute-Common Toxicity Criteria for AEs (version 4.0) at the baseline and at four-week intervals thereafter.
Statistical analysis
For PFS, the Kaplan-Meier method was used to estimate the survival curve. Assuming a threshold Median Survival Time (MST) of 3 months and an expected MST of 5.5 months, the required sample size was 48, at a significance level of 0.05 (one-sided) and power of 0.8. Therefore, the target sample size was set at 50. All statistical tests were two-sided and a 5% error was used in the PFS analysis.

Results
Patients
In total, 51 patients were recruited from seven institutes. Five patients were excluded: one patient refused the administration of Fulvestrant after registration, one was administered another drug before registration and three had a performance status of 2-4. Overall, 46 patients were analyzed.

The participants’ baseline characteristics are shown in Table 1. Their median age was 69 years. Recurrence was observed in 35 cases (76%) and de novo metastasis in 11 (24%), in whom the treatment lines were as follows second: 31, third: 10, and fourth: 5. All patients had ER-positive disease and 34 patients (73.9%) showed progesterone receptor-positivity. Two cases showed HER2-positivity (and ER-positivity). Recurrent metastasis was observed in 35 cases, with advanced disease observed in 11 (56.6%). Nineteen patients (41.3%) showed visceral involvement.

The median PFS was 8.5 months (95% confidence interval [CI]: 5.6-14.5 months) (Figure 1). The 90% CI was 5.6-14.5 months. The lower 90% CI (5.6 months) limit was higher than the threshold MST of 3 months, suggesting that this protocol was effective.

The ORR and CBR, as listed in Table 2, were 6.5% (95% CI: 1.4-17.9%) and 47.8% (95% CI: 32.9-63.1%), respectively.

The PFS duration in the recurrent metastasis cases (n=35) was 8.0 months (95% CI: 4.9-15.4), while that for the advanced disease cases (n=11) was 8.7 months (95% CI: 7.3-NA) (Figure 2a). Furthermore, the PFS associated with second-line (n=31), third-line (n=10) and fourth-line (n=5) ET was 8.1 months (95% CI: 4.9-15.4), 7.8 months (95% CI: 2.3-NA) and 14.5 months (95% CI: 13.4-NA), respectively. The durations from AMBC diagnosis to Ful-500 use in the second, third, and fourth-line ET groups were 8, 25, and 49 months, respectively.

Safety
Table 3 lists the incidence of prespecified AEs due to Ful-500 use. AEs were reported in 15 of 46 cases (32.6%). However, all the AEs were of grade 1 or 2. AEs of ≥ grade 2 included: injection site reactions: 4 (8.7%), back pain: 4 (8.7%), arthralgia: 3 (6.5%), and anorexia: 2 (4.3%). There were no notable changes in either the clinical chemistry or vital signs, and electrocardiography values.

Discussion
For AMBC patients, the sequential use of ETs, especially the use of a subsequent therapy with a mechanism of action that differs from that in the case of the prior therapy is important to obtain a beneficial effect in the maintenance of a good QOL and prolonged survival [25].
The sequential administration of first-line Anastrozole followed by tamoxifen is effective in the treatment of postmenopausal women with advanced breast cancer [26]. Previous studies have demonstrated the efficacy of Fulvestrant in the degradation of ERs when included in second-line ET or higher. Namely, Ful-500 is more effective than Ful-250 and non-steroidal AIs [13,17,18]. Additional data, which confirmed the dose escalation of Fulvestrant, determined that Ful-500 provides a statistically significant improvement in both PFS (6.5 months) and overall survival (22.8 months) without an increase in toxicity [17,18]. Eventually, the loading dose of Ful-500 (on days 1, 14 and 28, followed by administration every 28 days thereafter) is now the recommended dose. With the publication of the aforementioned reports, Fulvestrant use was approved in Japan in 2011. However, there is lack of adequate data on the efficacy of Ful-500 in clinical practice.

To clarify the real-world status of Ful-500 use in Japan, Kawaguchi et al. [19], conducted a large retrospective cohort study including 1,031 patients from 16 institutions [19]. That analysis, in which first-line treatment was provided to 2.0%, second-line ET to 22.7%, third-line ET to 26.7%, and ≥ fourth-line to 48.6% of patients, demonstrated a median Time to Failure (TTF) of 5.4 months. Multivariate analyses demonstrated there was a significant statistical association between a longer TTF and several characteristics such as earlier treatment line, duration from AMBC diagnosis to Ful-500 use greater than 3 years, absence of prior palliative chemotherapy, and disease-free interval greater than 2 years. They concluded that patients with ER-positive AMBC may benefit from Fulvestrant therapy early in their treatment course.

In MBC, metastatic lesions are located in various sites, particularly in non-measurable bone metastasis cases. In this study, the enrollment of patients with non-measurable lesions was allowed; in such cases, the unequivocal progression of non-CR/non-PD lesions was evaluated according to RECIST (version 1.1) criteria using a combination of clinical observation and several modalities such as CT, MRI, PET/CT, bone scintigraphy, and tumor marker level estimation. In this paper, we evaluated the real-world impact of Ful-500 for AMBC using a prospective cohort study of patients receiving second to fourth-line ET. In spite of the small sample size, the median PFS was 8.7 months, which was statistically significant; this may be attributed to the fact that our population comprised 33 patients (71.1%) who received second-line ET, which is totally different from the Safari study. In detail, the PFS values associated with each line of ET were: 8.1 months for second-line, 7.1 months for third-line, and 14.5 months for fourth-line ET. Interestingly, the PFS for fourth-line ET was longer than that for second and third-line ET. In terms of the duration from AMBC diagnosis to Ful-500 use, the values for second, third, and fourth-line ET were 8, 25, and 49 months, respectively.

In the ER-positive AMBC patients, the survival duration was about 4 years; in the setting of fourth-line ET (49 months), this duration is considerably long. In other words, patients requiring fourth-line therapy continued to have a high sensitivity to ET, resulting in longer disease-free survival rates [27,28]. Of note, among five patients receiving fourth-line ET, one had bilateral lung and cervical lymph node metastasis, suggesting that endocrine monotherapy may be effective so long as the function of the ER is normal and it is sensitive to estrogen irrespective of the metastatic site.

As seen in Table 3, AEs were observed in 15 of 46 cases (32.6%). They were all grades 1-2 AEs, with infusion-related reactions and back pain the most commonly cited (8.7%). This AE profile was recoverable and similar to that reported previously [17]. There was no case in which Ful-500 discontinuation was required owing to AE presentation. These results indicate that Ful-500 is safe for use and tolerable in patients with PS 0/1 requiring second to fourth-line ET, even in elderly populations.

Recent strategic advances for hormone-receptor positive AMBC include the establishment of molecular targeted agents. Combination therapy using Ful-500 and Palbociclib as second-line ET yielded a PFS of 9.5 months, with a 73% occurrence rate of grades 3-4 AEs [29,30]. The present study, accomplished under similar conditions, yielded PFS duration of 8.7 months with recoverable AEs. If Ful-500 monotherapy is effective, it may serve as an economical treatment option for AMBC. Namely, monotherapy using Ful-500 may be useful for ER-positive AMBC patients in the presence of hormone sensitivity.

In summary, Ful-500 was found to be effective and tolerable in ER-positive AMBC patients. Attention should be paid to the selection of therapeutic strategies based on the associated efficacy, QOL, and economic performance.

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Competing Financial Interests

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