Phase II Trial of Fulvestrant With Metronomic Capecitabine for Postmenopausal Women With Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer


Abstract

We present results of a phase II study of 41 patients with hormone-positive, HER2-negative metastatic breast cancer (MBC), who received fulvestrant and low-dose metronomic capecitabine. Primary end points were progression-free survival (PFS) and time to progression (TTP). Patients completed a median of 11 monthly treatment cycles, with median PFS of 14.98 months, and median TTP of 26.94 months, with treatment well-tolerated overall.

Background: In this phase II study, we explored efficacy and toxicity of combined endocrine and low-dose metronomic chemotherapy therapy consisting of fulvestrant and capecitabine in estrogen and/or progesterone receptor-positive, HER2-negative MBC. Patients and Methods: Patients with ≤ 1 previous hormonal treatment in the metastatic setting received an injection fulvestrant loading dose 500 mg on day 1, 250 mg on days 15 and 29 followed by 250 mg every 28 days along with continuous oral capecitabine in divided doses. The total fixed daily dose of capecitabine was either 1500 mg or 2000 mg, depending on the patient’s weight (< 80 kg vs. ≥ 80 kg). Primary end points were PFS and TTP. Toxicity was assessed by continuous evaluations of treatment-emergent adverse events (AEs) and changes from baseline in laboratory values. Results: Forty-one women, with a mean age of 64.5 years, were enrolled. Patients completed a median of 11 monthly treatment cycles. Median PFS was 14.98 months (95% confidence interval [CI], 7.26-upper limit [UL] not estimated) and median TTP was 26.94 months (95% CI, 7.26-UL not estimated). Median overall survival was 28.65 months (95% CI, 23.95-UL not estimated). Treatment was well tolerated with < 10% Grade 3 palmar-plantar erythrodysesthesia. Overall, the most frequent AEs were palmar-plantar erythrodysesthesia, fatigue, and nausea. Conclusion: Fulvestrant with metronomic capecitabine demonstrates substantial activity in hormone receptor-positive MBC and is well tolerated. Combined chemoendocrine approaches should be further explored considering the low toxicity of the combination with meaningful TTP.

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Introduction

Estrogen receptor (ER)-positive (ER+) metastatic breast cancer (MBC) presents a challenge for treatment because patients with exposure to previous hormonal therapy including aromatase inhibitor (AI) treatment ultimately develop resistant disease unresponsive to standard approaches to ER blockade. Fulvestrant (Faslodex, AstraZeneca Pharmaceuticals LP) is a selective ER downregulator with minimal agonist properties,1 and it has been approved for use in MBC for patients with disease progression after having received antiestrogen therapy. Two large randomized trials showed that fulvestrant (250 mg intramuscular injection every 28 days) had
similar efficacy to the AI, anastrozole, in advanced breast cancer. More recent studies demonstrated improved steady-state plasma concentrations using a loading dose schedule of fulvestrant 500 mg followed by 250 mg on days 14 and 28 with 250 mg every 28 days thereafter. Median time to steady-state with the loading dose of 500 mg was attained within 28 days compared with 3 to 6 months using the monthly 250-mg dose. In the recent phase III Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) trial, fulvestrant 500 mg every 28 days plus an additional 500 mg on day 14 of the first month only vs. 250 mg every 28 days were compared in patients with ER advanced breast cancer who experienced progression after previous endocrine therapy. The 500-mg dose produced a significant increase in progression-free survival (PFS) compared with the 250-mg dose (20% reduction in risk) without an associated increase in toxicity. At the time the current trial was initiated and conducted, the results from the CONFIRM trial were not available, and the 250-mg dose was the approved dose.

Capecitabine (Xeloda, Genentech USA, Inc) is an oral chemotherapy agent with known activity in MBC, and some investigators have suggested that it might be preferred over the taxanes because of its tolerability and relatively lower toxicity. Metronomic daily dosing of capecitabine can be especially useful for reducing toxicities without compromising efficacy. Taguchi et al used a low dose schedule of capecitabine as first-line therapy for MBC that recurred after previous treatment with anthracycline and taxane in 33 patients. They reported a median PFS of 6.9 months with overall survival (OS) of 24.8 months.

The combination of chemotherapy and endocrine therapy simultaneously was evaluated in the 1970s, using tamoxifen and intravenous chemotherapy regimens available at the time. No additional benefit was observed using the combination, and the concept was largely abandoned. However, with better understanding of the biology of endocrine resistance and more effective endocrine and chemotherapeutic agents, combination chemotherapy-endocrine therapy or combined endocrine therapy has been the focus of recurrent interest. A combination of everolimus, a mammalian target of rapamycin inhibitor, with the nonsteroidal AI, exemestane, was recently approved by the US Food and Drug Administration for endocrine-resistant hormone receptor-positive MBC. Three prospective studies have evaluated the combination of fulvestrant and an AI in postmenopausal women with advanced breast cancer; however, there are still no consistent data to support the use of combination endocrine therapy.

In this phase II study, the efficacy and safety of combining fulvestrant 250 mg on a loading dose schedule with daily low-dose capecitabine to treat MBC in postmenopausal women with ER or progesterone receptor-positive disease were investigated.

 Patients and Methods

Patients

Patients were recruited from 5 community oncology clinics in the United States associated with ACORN Research, LLC (Memphis, TN). Eligible patients were postmenopausal women with: histologically or cytologically confirmed, HER2-negative (−), ER and/or progesterone receptor-positive MBC; adequate hematologic, renal, and hepatic functioning; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; and no more than 1 previous endocrine therapy for MBC. Patients were excluded if they had: previous chemotherapy for MBC; radiotherapy within 2 weeks of enrollment; life expectancy less than 3 months; previous exposure to capecitabine or fulvestrant; or active brain metastases.

Study Design

This study was a phase II, multicenter, open-label, and single-arm combination treatment (fulvestrant with capecitabine) trial. The fulvestrant component comprised an initial loading dose of 500 mg on day 1 followed by 250 mg on days 15 and 29, which was followed by 250 mg every 28 days. The capecitabine component comprised daily oral capecitabine taken continuously twice per day for a total fixed dose of either 1500 mg (1000 mg morning and 500 mg evening) if the patient weighed < 80 kg or 2000 mg (1000 mg morning and evening) if the patient weighed ≥ 80 kg, with an additional reduction of 500 mg for patients with renal impairment. This dosing was selected to approximate half of the approved dose on a 2-week on, 1-week off schedule. One cycle was defined as a 28-day period.

Patients with stable or responding disease were treated until disease progression, intolerable toxicity, patient refusal to continue, or investigator decision to discontinue the patient per-protocol. Patients were removed from study treatment if for any reason they had a treatment delay or interruption for 3 weeks or more.

All study procedures were approved by the Western Institutional Review Board (Olympia, WA) and by local institutional review boards as required. Informed consent was obtained from each patient before enrollment.

Study End Points

The primary efficacy end points were PFS and time to progression (TTP). Secondary end points included overall response rate (ORR), defined as complete response (CR) plus partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.0; clinical benefit rate, defined as CR plus PR plus stable disease (SD) lasting at least 24 weeks according to RECIST guidelines; toxicity rates using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI CTCAE, v3.0); and symptom burden using patient-reported outcomes. OS was not a prespecified end point, but was also assessed.

Assessments

Radiologic assessments occurred at: screening, after every 2 cycles of treatment, and during posttreatment follow-up. CR or PR was confirmed in repeat imaging studies 4 to 8 weeks after initial response was documented.

Toxicity rates were assessed according to continuous evaluations of treatment-emergent adverse events (AEs) and changes from baseline in clinical laboratory test values (including a complete blood count, complete metabolic panel, cancer antigen 15-3 or 27,29), ECOG performance status, blood pressure, pulse, and physical examination findings. AEs were recorded and graded using the NCI CTCAE, v3.0. Patient-reported symptom burden was assessed according to patient-reported outcomes obtained from routine clinical administration of the Patient Care Monitor (PCM). PCM, version 2.0, is...
an 86-item self-report measure that is used to assess physical symptoms, psychological symptoms, and physical and social functioning, and asks patients to rate the severity of symptoms on an 11-point (0 to 10, “not a problem” to “as bad as possible”) Likert-type scale. In this study, PCM items were used to identify symptom severity ratings of ≥7, which corresponds to “severe” symptoms as reported by the patient. PCM data were available for most but not all patients. The focus of the analysis was items endorsed as severe by at least 4 patients.

**Statistical Methods**

Descriptive statistics including means and standard deviations for continuous variables, and frequencies and percentages for categorical variables, were reported for patient and disease-related characteristics. Kaplan-Meier survival analysis was used to estimate PFS, TTP, and OS. The median value for each time to event end point, and 95% confidence intervals, are reported. Percentages of patients experiencing AEs according to grade, and of patients experiencing severe symptom burden indicated by PCM item scores (≥7) are reported.

**Results**

Forty-one women with MBC participated in this phase II trial. The demographic and disease characteristics of the sample are shown in Table 1. The average age of the patients was 64.5 years. More than half (53.7%) were Caucasian, and 36.6% were African-American. Overall 17 of 41 patients (41.5%) were initially diagnosed with metastatic disease; the remaining patients were initially diagnosed at earlier stages of disease (24 of 41; 58.5%) but developed metastatic disease before enrollment in this study. All but 4 of the patients (37 of 41; 90.2%) had good performance status, with ECOG ratings of 0 to 1. By design, all patients were HER2/neu negative, and most cases were estrogen and progesterone receptor-positive.

Among the 24 patients diagnosed at an earlier stage of disease, patients received the following in the adjuvant setting: tamoxifen only, 8; AI only, 4; tamoxifen and AI, 6. Twelve patients had received 1 line of hormonal therapy in the metastatic setting (10 AI and 2 tamoxifen), of whom 9 had hormonal therapy in the adjuvant setting.

**Treatment Outcomes**

The median number of completed cycles of combined capecitabine with fulvestrant was 11, with a range from 2 to 32. Twenty-four patients (58.5%) had a baseline weight of <80 kg and 17 patients (41.5%) had a baseline weight of ≥80 kg. There was a significantly greater rate of capecitabine dose reduction in the ≥80 kg group than in the <80 kg group (65% vs. 13%, P = .0007), but the ≥80 kg group had greater exposure, with a median of 14 cycles, vs. just 5 cycles for the <80 kg group. Twenty patients (48.8%) completed 1 year of therapy, and 5 patients (12.2%) completed 2 years of therapy.

The median PFS in the sample was 14.98 months (95% confidence interval [CI], 7.26 months-upper limit not estimated).
Twenty-three patients experienced disease progression, 1 died, and 17 were censored in PFS analysis. Figure 1 shows the Kaplan-Meier estimate of the survival function for PFS (in months). The median TTP was 26.94 months (95% CI, 7.26 months-upper limit not estimated), with 20 patients censored in TTP analysis. Despite the incidental difference in median values, the survival curve for the TTP analysis (not shown) was very similar to that for PFS shown in Figure 1. The median OS in the sample was 28.65 months (95% CI, 23.95 months-upper limit not estimated), with 14 deaths, and 27 patients censored in the analysis (Fig. 2).

Responses rates are displayed in Table 2. Two patients had a CR and eight had a PR, yielding an ORR of 24.4% (95% CI, 10.0%-38.8%). The remaining patients included those with SD

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Tumor Response, n = 41&lt;sup&gt;b&lt;/sup&gt;</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td></td>
<td>2</td>
<td>4.9</td>
</tr>
<tr>
<td>Partial Response</td>
<td></td>
<td>8</td>
<td>19.5</td>
</tr>
<tr>
<td>Stable Disease</td>
<td></td>
<td>28</td>
<td>68.3</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td></td>
<td>3</td>
<td>7.3</td>
</tr>
<tr>
<td>Stable Disease ≥ 24 Weeks</td>
<td></td>
<td>14</td>
<td>34.1</td>
</tr>
</tbody>
</table>

Clinical Benefit Rate<sup>c</sup>: 24, 58.5

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.
<sup>a</sup>Total number of patients in the intent to treat population. Best overall response is defined as the best response across all time points.
<sup>b</sup>Clinical benefit rate calculated as CR + PR + SD ≥ 24 weeks.

Table 3 Treatment-Emergent AEs Occurring in ≥ 10% of Patients

<table>
<thead>
<tr>
<th>AE</th>
<th>Treatment Group: Capecitabine/Fulvestrant, n = 41&lt;sup&gt;b&lt;/sup&gt;</th>
<th>All Grades, n (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Grade 3, n (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Grade 4, n (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmar-Plantar Erythrodysesthesia</td>
<td></td>
<td>17 (41.5)</td>
<td>3 (7.3)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>16 (39.0)</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>14 (34.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td>10 (24.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>10 (24.4)</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>10 (24.4)</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Edema, Peripheral</td>
<td></td>
<td>10 (24.4)</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td></td>
<td>9 (22.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>9 (22.0)</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td>8 (19.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Back Pain</td>
<td></td>
<td>8 (19.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin Hyperpigmentation</td>
<td></td>
<td>8 (19.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>7 (17.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>7 (17.1)</td>
<td>2 (4.9)</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia, Peripheral</td>
<td></td>
<td>7 (17.1)</td>
<td>2 (4.9)</td>
<td>2 (4.9)</td>
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<tr>
<td>Neupathy, Peripheral</td>
<td></td>
<td>7 (17.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td></td>
<td>6 (14.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry Skin</td>
<td></td>
<td>5 (12.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td>5 (12.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td>5 (12.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>5 (12.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td></td>
<td>5 (12.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deep Vein Thrombosis</td>
<td></td>
<td>3 (7.3)</td>
<td>2 (4.9)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td></td>
<td>2 (4.9)</td>
<td>1 (2.4)</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

*Table includes all Grade 3 or 4 events occurring at least twice and any event that occurred at 10% or greater frequency. Patients were counted once per AE term. The highest AE grade was tabulated for patients with multiple events of the same AE term.
<sup>a</sup>Total number of patients.
<sup>b</sup>National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
Adverse Events and Patient-Reported Severe Events

None of the patients had dose reductions of fulvestrant. Dose reductions of capecitabine occurred in 14 (34.1%) patients. Most of these dose reductions (12 of 14; 85.7%) were because of palmar-plantar erythrodysesthesia. Two of the 12 patients had more than 1 dose reduction within the first 6 cycles of treatment. One patient had a dose reduction attributed to diarrhea and another patient’s dose reduction was because of elevated creatinine. Overall, only 2 patients discontinued therapy because of any treatment-related toxicity.

Table 3 shows a summary of the treatment-emergent AEs including all grade 3 or 4 events occurring at least twice and any event that occurred at a frequency of at least 10%. The most frequent events of any grade were palmar-plantar erythrodysesthesia (n = 17, 41.5%), followed by fatigue (n = 16, 39.0%) and nausea (n = 14, 34.1%). Overall, there were 13 (31.7%) patients who experienced any grade 3 event, but only 4 (9.8%) patients who experienced any grade 4 event. Palmar-plantar erythrodysesthesia was the most frequent grade 3 event (n = 3, 7.3%), and hypokalemia was the most frequent grade 4 event (n = 2, 4.9%).

Patient Care Monitor survey responses indicating severe symptoms are reported in Table 4. Severe fatigue was reported by 8 patients (26.7%) at some point during their treatment. Similarly, joint pain, muscle aches, and general pain were reported at the same frequency (n = 8, 26.7%). Not surprisingly, given the advanced disease stage and age of these patients, some PCM items related to functioning were also endorsed among 20% or more of patients as severe problems: attending a paid job, driving, performing hard work or activity, doing household work, and running.

Discussion

In this phase II study, the efficacy and toxicity of combined fulvestrant and low dose metronomic capecitabine in hormone-positive, HER2 MBC were investigated. Median PFS in this sample was 14.98 months. In general, the present regimen was well tolerated with a small degree of grade 3 palmar-plantar erythrodysesthesia (n = 3, 7.3%) related to capecitabine. Despite this, patients were able to tolerate capecitabine continuously with acceptable toxicity. No evidence of antagonism between endocrine and chemotherapy was observed in this study.

Patient-reported outcomes showed that fatigue and pain complaints were the most prominent problems (n = 8, 26.7%) reported at a severe level of complaint and 14% or more of patients reported severe practical difficulties with daily functioning tasks during treatment.

The combination of fulvestrant 500 mg loading dose was followed by 250 mg every 28 days along with daily low-dose capecitabine. The 250-mg dose is lower than that reported in the recent CONFIRM study of single-agent fulvestrant, by Di Leo et al, which compared fulvestrant with either standard dosing (250 mg) or high dosing (500 mg). Results in that study showed PFS to be 5.5 months and 6.5 months for standard and high dosing, respectively, and the 500-mg dose has since become the standard. At the time the current trial was initiated and conducted, however, these results were not available, hence the use of the lower, then-standard dosing. The CONFIRM trial also showed that after a loading dose, higher dose (500 mg) fulvestrant compared with lower dose (250 mg) every 28 days yielded a 20% reduction in risk of progression (P = .006), and there were no dose-dependent AEs with use of the higher monthly dose. Note that patients in the CONFIRM trial had to have progressed after previous endocrine therapy in the first-line setting, or within 1 year of treatment in the adjuvant setting. These inclusion criteria are somewhat more restrictive than those in the current study, and might account, in part, for the difference in observed PFS outcomes.

The optimal dose of capecitabine to use in a metronomic fashion has not been established. The present trial therefore used an empiric dosing schedule dichotomized according to weight. Other trials have used other approaches.

The fulvestrant arm in the Evaluation of Faslodex versus Exemestane Clinical Trial (EFFECT) trial reported by Chia and colleagues was comparable to the fulvestrant schedule in this study. Chia et al reported a median TTP of 3.7 months, compared with 26.94 months (95% CI, 7.26 months–upper limit not estimated) for the current sample. There are some notable differences between the Chia et al sample and the current study sample. The inclusion criteria in the EFFECT study required all patients to have had progressive or recurring disease after treatment with a nonsteroidal AI, and approximately 60% of patients in that study had 2 or more previous endocrine therapies. In contrast, half of the patients in the current sample had no previous hormone therapies.

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Capecitabine With Fulvestrant in MBC

Findings in the current study could also be considered in comparison with previous studies of single-agent low-dose capecitabine. As previously noted, Taguchi et al. reported a median PFS of 6.9 months for a low-dose capecitabine regimen. Their dosing schedule was 825 mg/m² twice daily for 21 days followed by a 7-day rest in a 28-day cycle. The only notable toxicities were grade 3 neutropenia (6%) and palmar-plantar erythrodysesthesia (15%). Bajetta et al. reported fewer toxicities in elderly MBC patients treated with capecitabine 1000 mg/m² twice daily for 14 days followed by a 7-day rest in 21-day cycles, compared with similar patients treated with capecitabine 1250 mg/m² twice daily. Efficacy in the low-dose schedule was comparable with the standard-dose schedule with PFS of 4 months.

Conclusion
The combination of fulvestrant 500 mg loading dose followed by 250 mg every 28 days along with daily low-dose capecitabine showed substantial clinical activity in this sample of postmenopausal MBC patients with ER+ and/or progesterone receptor-positive disease. This endocrine and chemotherapy treatment was also well tolerated. The ability of patients to continue this combination therapy for periods of 2 years or more without dose interruption speaks to the lack of cumulative toxicity in this low-dose approach. Indeed, the growing recognition of the heterogeneity of MBCs suggests hormone receptor-positive and -negative populations can coexist, making this approach a reasonable option for prolonged disease control.

Results from this phase II study and additional results from recent trials of fulvestrant suggest that the combination of daily metronomic capecitabine with fulvestrant (500 mg) should be further explored in hormone receptor-positive, HER2+ postmenopausal women with MBC.

Clinical Practice Points
- Combination chemoendocrine therapy was explored decades ago when both modalities offered limited options for simultaneous delivery, ER testing was not standardized, and before breast cancer heterogeneity was appreciated.
- Metronomic low-dose chemotherapy is well tolerated, can be delivered for extended periods, and might work by mechanisms alternative to higher dose cytotoxic agents. Additionally, single-agent endocrine therapy in patients previously treated with adjuvant hormone therapy provides less benefit than in endocrine-naive patients, probably because of acquired resistance and activation of alternative oncogenic pathways.
- This phase II trial used the combination of fulvestrant, a selective ER modulator, and low-dose continuous daily capecitabine, an antimitabolite, to treat advanced hormone receptor-positive breast cancer.
- The median PFS of 14.98 months, median TTP of 26.94 months, and clinical benefit rate of 58.5% compared favorably with published reports of endocrine therapy alone in similar patient populations.
- Toxicity was easily managed, and prolonged use of the regimen was well tolerated. This approach could be used in clinical practice in selected patients and deserves further exploration with optimal dosing of both agents.

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Disclosure
Dr Schwartzberg serves on the speaker’s bureau for Hoffmann-La Roche, Inc. All other authors state that they have no conflicts of interest.

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