

## Combining Fulvestrant with Low-Dose Capecitabine is Effective and Tolerable in Woman with Metastatic Breast Cancer

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Although the use of endocrine therapy in combination with intravenous chemotherapy has not been standardized, the combination of fulvestrant and chemotherapy may be promising. A 62-year-old woman came to our hospital's outpatient clinic with extensive ascites. Approximately 10 years earlier, she had undergone mastectomy and sentinel lymph node biopsy. Pathologically invasive lobular carcinoma, with a maximum diameter of 28 mm, had been diagnosed in the left breast. The cancer had a histological grade of 2, was positive for estrogen receptor (95% or more positive cells), and was negative for both progesterone receptor (less than 1% positive cells) and human epidermal growth factor receptor 2. For 5 years the patient underwent adjuvant endocrine therapy with tamoxifen and then with anastrozole. Four years 2 months after adjuvant endocrine therapy had been completed, she felt abdominal distention, and her symptoms gradually worsened. A series of intensive examinations indicated that the invasive lobular carcinoma had metastasized to the peritoneum, pleura, uterus, and bone. Aromatase inhibitor was administered as a first-line therapy for the metastatic disease and was accompanied by denosumab injected every 28 days. For 2 months after the start of treatment with anastrozole, the ascites did not decrease and tumor markers increased. Because anastrozole had not been effective, fulvestrant (500 mg) and low-dose capecitabine (500 mg) were administered for the first 21 days of a 28-day cycle; this regimen had been shown by a phase 2 trial to be effective and tolerable in patients with metastatic breast cancer. The patient felt an improvement in abdominal distention, and the tumor markers decreased 2 weeks after the start of this combination therapy. By 10 months after the start of the combined therapy the ascites had decreased and pleural effusion had completely disappeared. The uterine wall became thinner, and the endometrial cavity became smaller. Tumor markers continued decreasing. No adverse events were observed. The combination of fulvestrant and low-dose capecitabine is promising because of its efficacy and tolerability for the treatment of patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer.

(J Nippon Med Sch 2016; 83: 81–86)

**Key words:** fulvestrant, capecitabine, metastatic breast cancer

### Introduction

Fulvestrant is a selective estrogen receptor (ER) down-regulator, a so-called “pure antiestrogen,” that decreases ER expression with no agonistic effects<sup>1,2</sup>. The expression of ER is also affected by tamoxifen, a selective ER modulator that acts as a partial agonist<sup>1</sup>. Although tamoxifen is effective both in premenopausal and postmenopausal

women, fulvestrant is effective only in postmenopausal women<sup>3</sup>. Although fulvestrant has been used at a dose of 250 mg, at a dose of 500 mg fulvestrant has been shown to be more effective but no more toxic<sup>4,5</sup>. Currently, the standard administration of fulvestrant is a 500-mg intramuscular injection on days 1, 15, and 29 and every 28 days thereafter.

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The concurrent administration of tamoxifen and intravenous chemotherapy is no longer performed because synergistic efficacy was not demonstrated<sup>6</sup>. However, an oral fluorouracil prodrug, UFT (uracil and tegafur), has been used in combination with tamoxifen in adjuvant trials in Japan for patients with node-negative breast cancer<sup>6</sup>. In women with ER-positive breast cancer, the combination of UFT and tamoxifen seemed to yield better overall survivals than did each drug alone<sup>7</sup>. Currently, another oral fluorouracil prodrug, TS-1 (tegafur/gimeracil/oteracil potassium), is being investigated in a phase 3 study in Japan to determine whether its addition helps standard adjuvant endocrine therapy to inhibit recurrences in women with ER-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer (University Hospital Medical Information Network trial number, 000003969).

In an *in vitro* study, fulvestrant had a synergistic effect with doxorubicin, paclitaxel, docetaxel, vinorelbine, and fluorouracil; however, tamoxifen did not have such an effect<sup>8</sup>. Fulvestrant itself is a fully active drug that would not be expected to cause clinically significant drug interactions through the inhibition of cytochrome P450 (CYP)-mediated metabolism of co-administered agents<sup>9</sup>. Therefore, a concurrently administered drug is not likely to affect the safety or efficacy of fulvestrant<sup>9</sup>. However, tamoxifen is activated after it is metabolized to endoxifen, and its metabolic potency ranges widely due to gene polymorphism *CYP2D6*<sup>10</sup>. On the basis of these properties, fulvestrant might be a better choice than tamoxifen for use in combination with chemotherapy.

The efficacy and tolerability of the combination of fulvestrant and chemotherapy have been analyzed in only a single prospective trial. In a phase 2 trial, low doses of 1,500 mg (body weight <80 kg) or 2,000 mg of capecitabine were used in combination with a low dose (250 mg) of fulvestrant in 41 postmenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer<sup>11</sup>. The median time to progression (TTP) was 26.9 months, and the clinical benefit rate was 58.5%<sup>11</sup>. Accordingly, the combination of fulvestrant and capecitabine is a promising treatment for women with ER-positive, HER2-negative metastatic breast cancer.

We report a case of metastatic breast cancer in which combination treatment with fulvestrant and low-dose capecitabine was effective and tolerable.

### Case

A 62-year-old woman with extensive ascites came to our

outpatient clinic to consult about whether the ascites was a symptom of recurrent breast cancer. Nine years 10 months earlier, the patient had undergone breast-conserving surgery and sentinel lymph node biopsy. One month later she underwent an additional total mastectomy because of positive surgical margins. Pathologically invasive lobular carcinoma, with a maximum diameter of 28 mm, was diagnosed in the left breast. The carcinoma had a histological grade of 2, was positive for ER (95% or more positive cells), and was negative for both progesterone receptor (less than 1% positive cells) and HER2 (Herceptest<sup>®</sup>, score 0). The patient received tamoxifen for 2 years 9 months and then received anastrozole for 2 years 3 months to receive adjuvant endocrine therapy for a total of 5 years. Each year after surgery she underwent an annual check-up including palpation, mammography, and ultrasonography. Six months ago, a check-up revealed no abnormal locoregional findings. During the same time period, 4 years 2 months after adjuvant endocrine therapy had been completed, she felt abdominal distention, the symptoms of which gradually worsened.

Three months ago, while the patient consulted a physician in a hospital near her home, extensive ascites was diagnosed. She underwent a series of intensive examinations under hospitalization in our hospital's department of internal medicine. Computed tomography (CT) revealed extensive ascites (**Fig. 1a**) and minimal pleural effusion. The uterine wall was thickened, and the endometrial cavity contained a nonenhanced lesion (**Fig. 1b**). There were no abnormal findings in the liver, kidneys, adrenal glands, ovaries, or the lymph nodes of the peritoneal cavity. Magnetic resonance imaging of the pelvis revealed thickening of the myometrium and a fluid collection in the endometrial cavity. Diffusion-weighted images showed thickening of the peritoneum. The bone marrow of the pelvis was irregularly occupied by tumor-like infiltrations. Scintigraphy showed multiple metastases to the vertebrae, pelvic bones, femora, and humeri. Endoscopy had no abnormal findings in the esophagus, stomach, colon, or rectum.

When aspirated the ascites fluid was serous-bloody. Cytologic examination of the ascites fluid identified atypical cells; however, no definitive diagnosis was made. Cytologic examination of the endometrium, cervix, and vagina was negative. The concentrations of the tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 15-3, National Cancer Center-Stomach-439 (NCC-ST-439), and CA12-5 were 14.2 ng/mL, 66.1 U/mL, >5,000 U/mL, and 265.3 U/mL, respec-

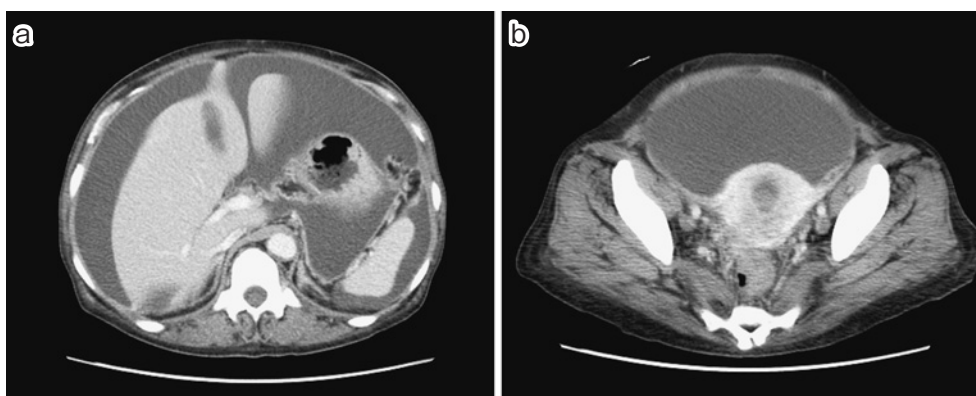


Fig. 1 Computed tomography (CT) of the abdomen (a) and pelvis (b). A large amount of ascites fluid was detected (a). The uterine wall was thickened, and the endometrial cavity was occupied by a nonenhanced lesion (b).

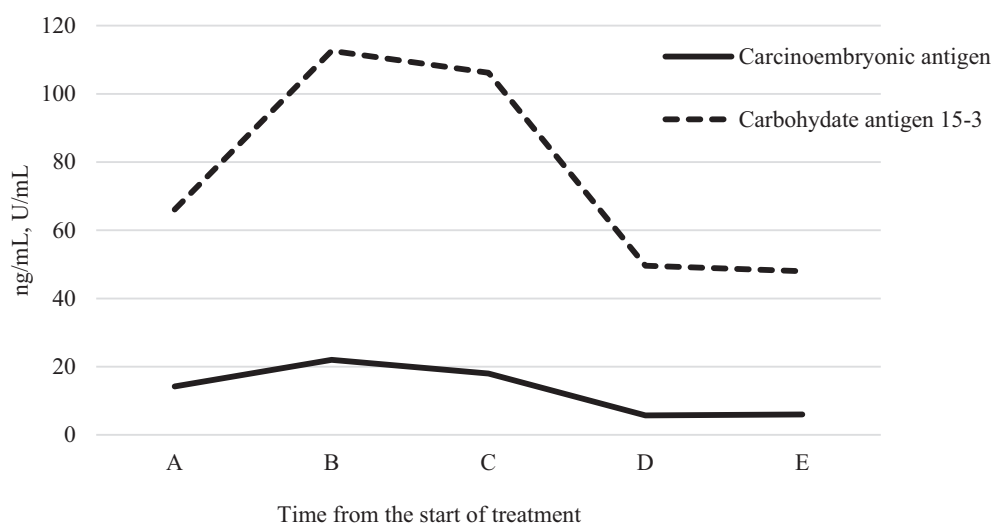


Fig. 2 Tumor makers. The concentrations of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 15-3 were 14.2 ng/mL and 66.1 U/mL, respectively, at baseline [A]. The concentrations of CEA and CA15-3 increased to 22.0 ng/mL and 112.6 U/mL, respectively, at 2 months after the start of anastrozole [B]. The concentrations of CEA and CA15-3 slightly decreased to 18.0 ng/mL and 106.2 U/mL, respectively, at 2 weeks after the start of combined fulvestrant with low-dose capecitabine [C]. The concentration of CEA decreased to 5.7 ng/mL at 6 months [D] and 6.0 ng/mL at 10 months [E] after the start of the combined therapy. The concentration of CA15-3 decreased to 49.6 U/mL at 6 months [D] and 48.0 U/mL at 10 months [E] after administration of the combined therapy.

tively, all of which were higher than normal ranges ( $\leq 5.0$  ng/mL,  $\leq 27.0$  U/mL,  $< 4.5$  U/mL, and  $\leq 35.0$  U/mL, respectively) (Fig. 2). Concentrations of CA19-9 and CA72-4 were 12.2 U/mL and 1.2 U/mL, respectively, both of which were within normal ranges ( $\leq 37.0$  U/mL and  $\leq 8.0$  U/mL, respectively). Drainage of the ascites fluid had been performed twice before the patient came to our outpatient clinic; the maximal volume of drained fluid was 4,700 mL.

On the basis of the above findings, we concluded that

the carcinoma of the left breast had metastasized to peritoneum, pleura, uterus, and bone. These metastatic patterns were considered typical of invasive lobular carcinoma of the breast.

A large amount of ascites fluid resulted in low activity in the patient's daily life; therefore, chemotherapy, such as an anthracycline or a taxane, was considered. However, the primary tumor was ER-positive and HER2-negative, and the disease was not life threatening. Therefore, endocrine therapy was considered optimal as a first-

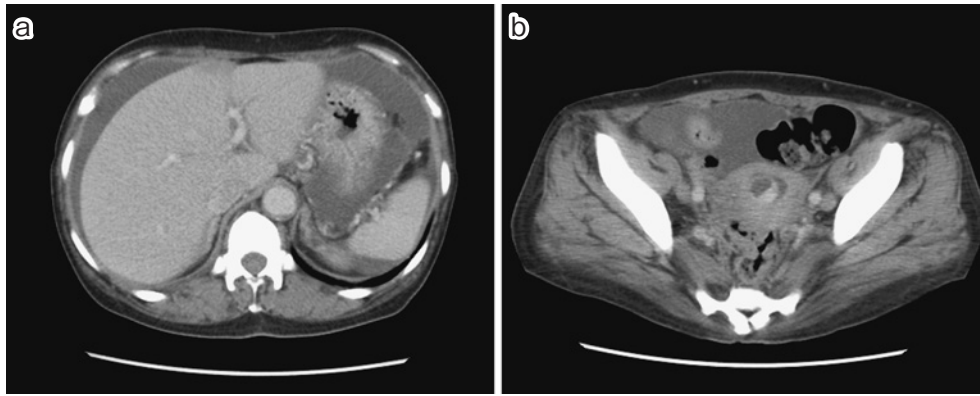


Fig. 3. Computed tomography of the abdomen (a) and pelvis (b). The ascites improved (a), and the uterine wall became thinner (b).

line therapy for the metastatic disease, accompanied by denosumab subcutaneously injected every 4 weeks. Tamoxifen or aromatase inhibitors were judged to be appropriate for this case because more than 4 years had passed since the completion of 5 years of adjuvant endocrine therapy, which had included tamoxifen and anastrozole. We chose anastrozole, which was considered to be more effective than tamoxifen. For 2 months after the start of treatment with anastrozole, the volume of the ascites had not begun to decrease. Drainage of the ascites fluid was performed 3 times during this period, and the maximal volume of drainage was 6,000 mL. The concentrations of the tumor markers CEA and CA15-3 had increased to 22.0 ng/mL and 112.6 U/mL, respectively (Fig. 2). Therefore, anastrozole was considered to have been ineffective in the present case.

As a second-line therapy, chemotherapy was considered optimal, because anastrozole had been ineffective and the ascites should have rapidly improved. However, the patient wanted to avoid hair loss. Accordingly, fulvestrant was considered suitable as a second-line endocrine therapy; however, it was not likely to rapidly decrease the volume of the ascites. Therefore, we chose to the combination of fulvestrant and capecitabine because a phase 2 trial had found that this regimen was effective and tolerable for patients with metastatic breast cancer. In this phase 2 trial, fulvestrant was administered at a low dose of 250 mg, and capecitabine was administered daily without interruption at low doses of 1,500 mg (body weight <80 kg) and 2,000 mg (body weight ≥80 kg). In the present case, 500 mg of fulvestrant was intramuscularly injected on days 1, 15, and 29 and every 28 days thereafter. Capecitabine, 1,800 mg, was administered daily for 21 days followed by a 7-day rest period in a 28-

day cycle. The daily dose of 1,500 mg of capecitabine administered without interruption was similar to the daily dose of 2,000 mg of capecitabine administered for 21 days in a 28-day cycle. In Japan, capecitabine is administered only with a tablet containing 300 mg. Because our patient's body weight was approximately 48 kg, 1,800 mg (6 tablets) of capecitabine was considered suitable.

After this combination therapy was started the patient felt slight improvement of abdominal distention, and by 2 weeks after the start the concentrations of CEA and CA 15-3 had decreased to 18.0 ng/mL and 106.2 U/mL, respectively, (Fig. 2). The ascites was drained 2 times during the month after the start of combination therapy, and the maximal volume drained was 3,500 mL. No further drainage was needed. The ascites had decreased by 10 months after the start of combination therapy (Fig. 3a), and pleural effusion had completely disappeared. Also during this time, the uterine wall became thinner (Fig. 3 b) and the endometrial cavity became smaller. Tumor markers had decreased in concentration for 10 months after the start of combined therapy (Fig. 2). No side effects were observed by physicians or complained of by the patient during the above-described period.

### Discussion

In the present case, the combination of fulvestrant and low-dose capecitabine was effective and well tolerated. However, a possible question in this case is whether each drug was itself effective. A randomized phase 2 study comparing the 2 drugs as first-line endocrine therapy agents in postmenopausal women with advanced, hormone receptor-positive breast cancer showed that the median TTP was 23.4 months with 500-mg fulvestrant and 13.1 months with 1-mg anastrozole, a 34% reduction in

risk of progression (hazard ratio, 0.66;  $P=0.01$ )<sup>12</sup>. A forest plot representing TTP, according to the predefined covariates, indicated that fulvestrant was significantly more effective than anastrozole in patients with no visceral involvement or prior chemotherapy<sup>12</sup>. The present patient had no visceral involvement and had not previously received chemotherapy; therefore, fulvestrant might have been more effective than anastrozole. In addition, the use of anastrozole as an adjuvant endocrine therapy might have led to resistance to anastrozole. The above suggests that fulvestrant alone might have been effective in the present case, whereas capecitabine might have had a synergistic effect.

In the present case, capecitabine was administered in a 28-day cycle at a dose of 1,800 mg (approximately 1,300 mg/m<sup>2</sup>) per day for 21 days and was then not administered for a 7-day rest period. A Japanese capecitabine package insert lists 2 cycles of capecitabine administration for patients with advanced or recurrent breast cancer. In a 28-day cycle 1,800, 2,400, or 3,000 mg of capecitabine is administered daily for 21 days and then not administered for a 7-day rest period for patients with a body surface of <1.31, ≥1.31 to <1.64, or ≥1.64 m<sup>2</sup>, respectively. In a 21-day cycle 3,000, 3,600, 4,200, or 4,800 mg of capecitabine is administered daily for 14 days and then not administered for a 7-day rest period in patients with a body surface of <1.33, ≥1.33 to <1.57, ≥1.57 to <1.81, or ≥1.81 m<sup>2</sup>, respectively. Therefore, our patient should have received 2,400 mg of capecitabine daily for 21 days of the 28-day cycle because her body surface was approximately 1.4 m<sup>2</sup>. Taguchi et al.<sup>13</sup> have reported that a capecitabine dose of 1,650 mg/m<sup>2</sup> was administered for 21 days of a 28-day cycle as a first-line therapy for a patient with metastatic breast cancer that recurred after adjuvant chemotherapy with an anthracycline or a taxane. They reported a median progression-free survival of 6.9 months and a median overall survival of 24.8 months. Stockler et al.<sup>14</sup> have reported that the following 3 treatments have the same efficacy as a first-line chemotherapy for metastatic breast cancer: 2,000 mg/m<sup>2</sup> of capecitabine administered for 14 days in a 21-day cycle, 1,300 mg/m<sup>2</sup> of capecitabine administered without interruption, and a classical regimen of cyclophosphamide, methotrexate, and fluorouracil. Leonard et al.<sup>15</sup> have reviewed clinical trials of capecitabine for metastatic breast cancer, including the studies described earlier. They concluded that the dose of capecitabine can be reduced to minimize adverse events without compromising efficacy. They recommended a starting daily dose of 2,000 mg/m<sup>2</sup>. Compared

with these recommended or licensed setting doses, the dose of capecitabine administered to the present patient was a low 1,800 mg (approximately 1,300 mg/m<sup>2</sup>). However, the capecitabine starting dose of approximately 1,300 mg/m<sup>2</sup> administered to our patient has not been clinically studied as a capecitabine monotherapy. Therefore, whether capecitabine is effective, when used alone at the dose of the present case, has not been clarified.

Schwartzberg et al.<sup>11</sup> have performed a phase 2 trial to examine the efficacy and tolerability of fulvestrant combined with low-dose capecitabine in 41 women with hormone receptor-positive, HER2-negative metastatic breast cancer; they reported a median TTP of 26.9 months, a median overall survival of 28.7 months, a complete response rate of 4.9%, a partial response rate of 19.5%, a clinical benefit rate of 58.5%, and a progressive disease rate of 7.3%. In their study, fulvestrant was administered at an initial loading dose of 500 mg on day 1 and then at a dose of 250 mg on days 15 and 29 and every 28 days thereafter. Capecitabine was administered daily without interruption at a dose of either 1,500 mg (body weight <80 kg) or 2,000 mg (body weight ≥80 kg). If the daily capecitabine doses are changed to adjust to our administration method, 1,500 and 2,000 mg of daily capecitabine are comparable to 2,000 and 2,667 mg, respectively. Fulvestrant was administered at a higher dose in the present case than in the above phase 2 study; whereas the daily capecitabine dose of 1,800 mg in the present case was similar to the daily dose of 2,000 mg (body weight <80 kg) in the phase 2 study of Schwartzberg et al.<sup>11</sup>. Therefore, our combination of fulvestrant and low-dose capecitabine might have been more effective than the regimen used in the phase 2 trial.

In the present case, no adverse events were observed for 10 months after the start of the combination therapy. Adverse events after treatment with 500 mg of fulvestrant have been reported by Robertson et al.<sup>12</sup>; with a median follow-up of 8 months the events included bone pain (13.9%), hot flash (12.9%), nausea (10.9%), arthralgia (9.9%), constipation (9.9%), vomiting (8.9%), dyspnea (8.9%), injection-site pain (5.0%), hyperhidrosis (4.0%), and urinary tract infection (4%). These findings suggest that fulvestrant can be safely administered with no severe side effects. In the phase 2 trial by Schwartzberg et al. of the combination of fulvestrant and low-dose capecitabine<sup>11</sup>, the most common side effect with a median follow-up period of 11 months, which was similar to the follow-up period of 10 months of the present case, was palmar-plantar erythrodysesthesia, which was observed



in 48.8% of patients and was followed by fatigue, 41.5%; nausea, 34.1%; diarrhea, 26.8%; headache, 26.8%; edema, 26.8%; cough, 24.4%; and vomiting, 24.4%; however, almost all were grade 1, according to the Common Terminology Criteria for Adverse Events, Version 3.0. These findings suggest that the additional administration of capecitabine with fulvestrant does not lead to any severe adverse events. Therefore, the combination of fulvestrant and low-dose capecitabine can be safely administered to treat metastatic breast cancer.

For the treatment of breast cancer, several molecular targeting drugs have recently been examined in combination with endocrine therapy<sup>3</sup>. One of the most suitable agents to combine with fulvestrant, as suggested by the present case study and previous studies, is low-dose capecitabine. However, the optimal dose of capecitabine, when combined with 500 mg of fulvestrant, should be determined in future clinical trials. In conclusion, we believe that the combination of fulvestrant and low-dose capecitabine is promising, because of its efficacy and tolerability, for the treatment of patients with ER-positive, HER2-negative metastatic breast cancer.

**Conflict of Interest:** The authors declare no conflict of interest.

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(Received, August 8, 2015)

(Accepted, August 13, 2015)