A Phase II Study of Adjuvant Chemotherapy of Tegafur–Uracil for Patients with Breast Cancer with HER2-negative Pathologic Residual Invasive Disease After Neoadjuvant Chemotherapy

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Abstract. *Background:* There is no consensus on the need for adjuvant chemotherapy for patients with pathological residual invasive breast cancer (non-pCR) after neoadjuvant chemotherapy (NAC). We evaluated the tolerability and safety of tegafur-uracil (UFT) as adjuvant chemotherapy for patients with human epidermal growth factor receptor 2-negative breast cancer that resulted in non-pCR after NAC. *Patients and Methods:* We treated patients with 270 mg/m² UFT per day for 2 years after definitive surgery and radiotherapy, if necessary. In cases with hormone-sensitive cancer, patients received concurrent endocrine therapy. The primary end-point was the rate of completion of scheduled UFT therapy. Secondary end-points included safety and disease-free survival. *Results:* Twenty-one out of 29 patients (72%) completed the scheduled therapy. Eight patients discontinued the study treatment because of disease recurrence, toxicities, and patients' wish. Excluding liver dysfunction, adverse events were quite mild. *Conclusion:* Adjuvant UFT therapy after NAC was feasible and safe.

Neoadjuvant chemotherapy (NAC) is widely used for both locally advanced and early-stage breast cancer. The advantages of NAC include determining tumor responses to specific treatment regimens in clinical practice and providing

an opportunity for down-staging to avoid mastectomy for inoperable tumors or breast-conserving surgery in cases originally requiring mastectomy (1, 2). Anthracyclines and taxanes have been used as the standard chemotherapeutic regimens for breast cancer, however, tumoral estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) statuses are important predictors of response to chemotherapy (3-5). Sensitivity to NAC is lower in ER-positive and HER2-negative cancer than in other subtypes. An earlier study of NAC with anthracyclines and taxanes reported an approximately 25% pathological complete response (pCR) rate in cases of operable breast cancer without taking in mind the ER and HER2 status (6). Furthermore, patients achieving pCR have a more favorable prognosis than patients with pathological residual invasive disease (non-pCR) (6-8). Adjuvant endocrine therapy for ER-positive breast cancer and anti-HER2 therapy (*e.g.* Trastuzumab) for HER2-positive breast cancer after NAC currently represent the gold-standard of care. There is a lack of consensus regarding the requirement for an adjuvant chemotherapy in cases with non-pCR after NAC; however, further chemotherapy may improve patient outcomes. Adjuvant chemotherapy is typically appropriate in patients with non-pCR because patients with operable breast cancer frequently experience tumor recurrence approximately 2 years after initial surgery (9).

Long-term, daily oral treatment with tegafur-uracil (UFT) is widely used as an adjuvant chemotherapy for breast, gastric, and colorectal cancer in Japan. (10). A pooled analysis of six randomized, controlled trials demonstrated the survival benefits of adjuvant UFT plus tamoxifen compared to tamoxifen alone for ER-positive early breast cancer (11). Moreover, two randomized, controlled trials demonstrated that UFT therapy for 2 years had similar efficacy to six cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)

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(12, 13). A combined analysis of these trials demonstrated that UFT was non-inferior to CMF in terms of inhibiting the recurrence of ER-positive, early breast cancer (14). UFT therapy is associated with a lower rate of adverse events (*e.g.* gastrointestinal symptoms, bone marrow suppression, and hair loss) and better quality of life compared with CMF therapy (10, 12). However, the safety of UFT therapy in patients previously treated with NAC remains unknown.

Therefore, we evaluated the tolerability and safety of adjuvant UFT chemotherapy for 2 years in patients with HER2-negative breast cancer with non-pCR after standard anthracycline- and taxane-based NAC to assess the preliminary efficacy of UFT therapy.

Patients and Methods

This present study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Osaka Medical College (approval number: 10-798). All the patients provided written informed consent. This study was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN00003835).

Patients. This study was a single-center, prospective, open-label, single-arm, phase II clinical trial. Eligible patients were females aged ≥ 20 years with HER2-negative operable breast cancer or locally advanced breast cancer that was suitable for definitive surgery after NAC with anthracycline and taxane. Moreover, all the patients were required to have non-pCR that was defined as no histological evidence of residual invasive tumor cells in the breast or axillary lymph nodes (ypT0/Tis and ypN0), according to histological assessments of surgical specimens. Immunohistochemical analyses for ER, progesterone receptor (PgR), and HER2 were performed for all tumors. Tumors with $\geq 1\%$ positively stained tumor cells were classified as positive for ER and PgR. HER2 negativity was defined as 0 or 1+ staining intensity using immunohistochemistry (IHC) or in case with 2+ by IHC with negative for *HER2* gene amplification by fluorescence *in situ* hybridization (FISH). A FISH ratio of <1.8 was considered negative. Patients were required to have an Eastern Cooperative Oncology Group performance status of <2 , adequate organ function [aspartate transaminase (AST), alanine transaminase (ALT), and bilirubin levels at ≤ 1.5 -times the upper limit of normal; leukocyte count of $\geq 3,000/\text{ml}$; neutrophil count of $\geq 2,000/\text{ml}$; thrombocyte count of $\geq 10 \times 10^4/\text{ml}$; serum creatinine level of $\leq 1.5 \text{ mg/dl}$; and normal cardiac function on electrocardiography], and no carry-over grade 2 or higher adverse events (except for alopecia) from NAC. Patients with a confirmed infection, serious concomitant illness (*e.g.* severe cardiovascular disease, uncontrolled diabetes, malignant hypertension, or hemorrhagic disease), active concomitant malignancy, brain metastasis, history of severe drug allergy, or previous treatment with oral CMF-based chemotherapy were excluded from this study. Pregnant and lactating women were also excluded. Mammography, ultrasonography, magnetic resonance imaging, or computed tomography was used to determine the presence of tumors.

Treatment. Each patient received 270 mg/m^2 UFT per day for 2 years (Table I). Toxicities were evaluated on a monthly basis using the National Cancer Institute Common Terminology Criteria for

Table I. Dose and administration of tegafur-uracil.

Body surface area (m^2)	Daily dose (mg)	Morning-evening (mg)
<1.3	300	200-100
1.3-1.67	400	200-200
≥ 1.67	500	300-200

Table II. Dose reduction of tegafur-uracil per day.

Body surface area (m^2)	Starting dose (mg)	1st step (mg)	2nd step (mg)
<1.3	300	Discontinued	-
1.3-1.67	400	300	Discontinued
≥ 1.67	500	400	300

Adverse Events (version 4.0) (15) and blood examinations throughout the treatment. Treatment was withheld for hematological toxicities, including leukocyte count of $<3,000/\text{ml}$, thrombocyte count of $<7.5 \times 10^4/\text{ml}$, hemoglobin level of $<9.0 \text{ g/dl}$, AST/ALT level of $\geq 100 \text{ IU/l}$, bilirubin level of $\geq 2.0 \text{ mg/dl}$, or grade 2 or higher non-hematological toxicities (anorexia, nausea, vomiting, diarrhea, and stomatitis), until improvement of these toxicities was confirmed. Once adverse events (AEs) had improved following treatment interruption, the UFT dose was reduced from the initial dose at the discretion of the treating physician. The UFT dose reductions are shown in Table II. Study treatment was discontinued in cases of disease progression or unacceptable toxicity. Supportive care was provided according to standard practices. All the patients with ER-positive tumors concurrently underwent UFT therapy with adjuvant tamoxifen or aromatase inhibitor endocrine therapy (postmenopausal women only). Additional treatment with a luteinizing hormone-releasing hormone analog could be provided to premenopausal patients. UFT administration was initiated after radiotherapy in patients requiring postoperative radiotherapy.

Study endpoints. The primary study endpoint was the rate of completion of scheduled adjuvant UFT therapy after 2 years. Secondary endpoints included safety and disease-free survival (DFS) rate. DFS was defined as the time from the initiation of UFT therapy to either the first recurrence or relapse, second cancer, or death.

Statistical analyses. As this trial was an exploratory study to evaluate the utility of continuous adjuvant UFT therapy in patients previously treated with NAC and there are currently no data from previous studies evaluating the tolerability of adjuvant UFT as a primary endpoint, we did not calculate a formal sample size using statistical data from previous comparable studies. Moreover, we considered that a number of cases were required for further exploratory analyses. Consequently, accrual of 50 patients was planned for this study. DFS was calculated using the Kaplan-Meier method. Statistical analyses were performed using SAS version 11.0 (SAS Institute, Cary, NC, USA).

Table III. Patient characteristics.

Characteristic	No. of patients (n=30)
Median age, years (range)	51 (29-67)
Performance status	
0	30 (100%)
1	0 (0%)
Menopausal status	
Premenopausal	14 (47%)
Postmenopausal	16 (53%)
Clinical tumor stage	
T1	4 (13%)
T2	13 (43%)
T3	7 (23%)
T4	6 (20%)
Clinical nodal stage	
N0	5 (17%)
N1	24 (80%)
N2	1 (3%)
Clinical stage	
I	3 (10%)
II	14 (47%)
IIIA	7 (23%)
IIIB	6 (20%)
ER status	
Positive	21 (70%)
Negative	9 (30%)
PgR status	
Positive	17 (57%)
Negative	13 (43%)
Triple-negative breast cancer	
Yes	8 (27%)
No	22 (73%)
Neoadjuvant chemotherapy	
FEC→docetaxel	28 (93%)
Docetaxel→FEC	2 (7%)

ER: Estrogen receptor; PgR: progesterone receptor; FEC: 5-fluorouracil, epirubicin, cyclophosphamide.

Results

Patient population. Because of a slow accrual rate to this study, we terminated the entry of patients before reaching the target number. A total of 30 patients were enrolled from September 2010 to March 2014. One patient withdrew consent before receiving the study treatment. Thus, the data of 29 patients were included in the end-point analyses of this study. Patient characteristics are shown in Table III. The median age of the patients was 51 years (range=29-67 years). Fourteen patients (47%) and 13 patients (43%) had stage II and III breast cancer, respectively. Of 30 patients, 21 (70%) had ER-positive breast cancer and 17 (57%) had PgR-positive breast cancer. Eight (27%) patients had ER-negative, PgR-negative, and HER2-negative breast cancer (triple-negative breast cancer, TNBC). We administered the

Table IV. Most common treatment-related adverse events (n=29).

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Hematological, n (%)				
Leucopenia	3 (10%)	7 (24%)	1 (3%)	0
Neutropenia	1 (3%)	4 (14%)	1 (3%)	0
Anemia	3 (10%)	0	0	0
Thrombocytopenia	4 (14%)	0	0	0
Hyperbilirubinemia	6 (21%)	3 (10%)	0	0
Alanineaminotransferase	7 (24%)	1 (3%)	2 (7%)	0
Aspartateaminotransferase	10 (34%)	1 (3%)	1 (3%)	0
Hyperuricemia	1 (3%)	0	0	0
Non-hematological, n (%)				
Fatigue	8 (28%)	0	0	-
Anorexia	5 (17%)	1 (3%)	0	0
Nausea	4 (14%)	0	0	-
Vomiting	0	0	0	0
Stomatitis	1 (3%)	1 (3%)	0	0
Dysgeusia	3 (10%)	2 (7%)	0	0
Diarrhea	4 (14%)	0	0	0
Rash	2 (7%)	1 (3%)	0	0
Skin hyperpigmentation	12 (41%)	1 (3%)	-	-

combination of CMF, epirubicin, and cyclophosphamide every 3 weeks (*q3w*) for four cycles and docetaxel *q3w* for four cycles to all patients as NAC.

Treatment administration and study completion. Initial doses of UFT were 400 mg and 500 mg in 24 and 5 patients, respectively. Eleven patients (38%) required dose reduction or interruption. Of these, eight patients (28%) required first-step dose reductions of UFT because of neutropenia (n=2), hyperbilirubinemia (n=3), elevated AST/ALT levels (n=1), and diarrhea (n=1). Interruptions of UFT therapy occurred in 31% of patients (9 out of 29 patients) because of leucopenia (n=2), neutropenia (n=1), elevated AST/ALT levels (n=2), hyperbilirubinemia (n=1), fatigue (n=1), stomatitis (n=1), and rash (n=1). A total of 21 patients (72%) completed the scheduled adjuvant UFT therapy with or without dose reductions. The rate of compliance without dose reduction was 55% (16 out of 29 patients). Eight patients discontinued the study treatment because of disease recurrence (n=1), delayed improvement of elevated AST/ALT levels (n=2), dysgeusia (n=1), rash (n=1), deep vein thrombosis due to tamoxifen (n=1), and patient wish (n=2). The mean total UFT dose was 79.4% of the target dose. After a median follow-up of 4.2 years (range=2.5-6.1 years), the DFS rate was 82%.

Safety profile. The incidences of treatment-related AEs are shown Table IV. Overall, AEs related to UFT therapy were mild in this study. Elevated AST and ALT levels were the

most frequent grade 3 AEs that were observed in 7% and 3% of patients, respectively. Grade 3 leucopenia and neutropenia were both observed in 3% of patients. We observed important common non-hematological toxicities of various grades, including anorexia, stomatitis, dysgeusia, rash, and skin hyperpigmentation. No grade 3 or greater non-hematological AEs or unexpected serious AEs were observed in this study.

Discussion

In this study, we evaluated the tolerability and safety of UFT as an adjuvant chemotherapy in patients with HER2-negative breast cancer with non-pCR after standard anthracycline- and taxane-based NAC. The rate of completion of scheduled adjuvant UFT therapy after 2 years (the primary study endpoint) was 72% (21 out of 29 patients). Furthermore, the rate of compliance without dose reduction was 55% (16 out of 29 patients). These findings are comparable with previous studies using the same regimen. The National Surgical Adjuvant Study for Breast Cancer 01 Trial compared the efficacy of six cycles of classical cyclophosphamide, methotrexate, and CMF with 2 years of UFT in patients with node-negative, high-risk breast cancer and reported a 64% compliance rate with or without dose reduction at 2 years in the UFT arm (12). In addition, the mean total UFT dose of 79.4% of the target dose in this study was comparable with a previous randomized study that compared UFT therapy for 2 years with classical CMF in patients with node-positive breast cancer (75%) (13).

Currently, adjuvant endocrine therapy for ER-positive and anti-HER2 therapy for HER2-positive breast cancer remain the standard-of-care, irrespective of the response (pCR or non-pCR) to NAC. In contrast, additional adjuvant chemotherapy in cases with pCR may represent over-treatment; however, further chemotherapeutic treatment may improve patient outcome in non-pCR cases. Recently, differences in response to NAC have been demonstrated to affect patient outcomes among certain subtypes of breast cancer. In high-risk ER-positive and HER2-negative (*e.g.* high-grade, high Ki-67 index) breast cancer and TNBC, pCR cases may have a more favorable prognosis than non-pCR cases (16, 17). As tumor recurrence often occurs approximately 2 years after initial surgery in these subtypes of breast cancer, adjuvant UFT therapy may be reasonable in non-pCR cases. Experimental evidence suggests that the prevention of recurrence by UFT involves the inhibition of angiogenesis in addition to the cytotoxic activity of fluorouracil (18). Long-term treatment with UFT may prolong the dormant status of micrometastases, thereby preventing recurrence.

AEs related to UFT therapy were quite mild in this study. Although we observed grade 3 hematological toxicities, there were no cases of grade 4 hematological toxicities or grade 3 or higher non-hematological toxicities. Elevated AST and ALT levels were the most frequent grade 3 AEs, observed in 7% and 3% of patients, respectively. Grade 3 leucopenia and

neutropenia were both observed in 3% of patients. These findings corroborate the findings of previous randomized studies (12, 13). Despite the concurrent use of UFT and endocrine therapy in patients with ER-positive breast cancer in this study, no increase in the incidence of AEs related to UFT were observed with the combination of these agents. Although oral fluoropyrimidines, such as UFT, are generally considered to be associated with a relatively low frequency of AEs, the incidence of liver dysfunction requires attention. Therefore, patients who receive UFT or other oral fluoropyrimidine therapy should be closely monitored for liver toxicity and undergo regular liver function tests.

The major limitation of this study was the relatively small sample size from a single institution. In addition, we were unable to set a predefined sample size according to statistical data from previous studies. We were also unable to meet the planned sample size. A further limitation was the lack of quality-of-life assessments, which have utility in estimating the feasibility of the study treatment. However, to the best of our knowledge, this is the first report evaluating the tolerability and safety of UFT in the adjuvant setting for patients who were previously treated with anthracycline- and taxane-based NAC.

In conclusion, adjuvant UFT therapy for 2 years in patients previously treated with anthracycline- and taxane-based NAC is well tolerable with a low incidence of adverse events related to toxicity. Large randomized trials are warranted to evaluate the efficacy of UFT as an adjuvant chemotherapy. Regarding the efficacy of oral fluoropyrimidines as an adjuvant chemotherapy, Toi *et al.* reported the results of phase III clinical trial that showed that capecitabine improves survival outcomes for non-pCR cases after NAC (19). Although potentially promising, it is important to consider the benefits and toxicity of additional adjuvant chemotherapy in patient populations similar to that of this study. Accordingly, methods for predicting the therapeutic benefit of such treatment regimens should also be investigated.

Conflicts of Interest

The Authors have stated that they have no conflicts of interest in regard to this study.

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