Original Study

Phase II Study of S-1 Combined With Low-Dose Docetaxel as Neoadjuvant Chemotherapy for Operable Breast Cancer Patients (N-1 Study)

Misako Nakagawa,[1] Mayumi Ikeuchi,[1] Masami Morimoto,[1] Hirokazu Takechi,[1] Hiroaki Toba,[1] Takahiro Yoshida,[1] Kazumasa Okumura,[1] Naoki Hino,[2] Aya Nishisho,[2] Akira Tangoku[1]

Abstract

Efficacy of S-1 (Taiho Pharmaceutical Co, Tokyo, Japan) used in combination with docetaxel (S-1+DOC) for breast cancer was evaluated. After 4 cycles of S-1+DOC, patients with a complete response (CR) underwent surgery, and those with partial response underwent 4 more cycles. Patients with stable disease or progressive disease received epirubicin and cyclophosphamide or trastuzumab and paclitaxel. The pathological CR rate was 29 patients [34.9%], and 8 patients [19.5%] for patients with luminal type breast cancer. S-1+DOC was expected to be an effective chemotherapy for luminal type breast cancer.

Background: To improve the pathological complete response (pCR) rate, we devised new neoadjuvant chemotherapy. Efficacy and safety of the oral fluoropyrimidine derivative S-1 (Taiho Pharmaceutical Co, Tokyo, Japan) combined with low-dose docetaxel (S-1+DOC) were evaluated. **Patients and Methods:** Patients were treated with docetaxel (40 mg/m^2 intravenously on day 1) and S-1 (40 mg/m^2 orally twice per day on days 1-14) every 3 weeks for 4 cycles. In accord with the Response Evaluation Criteria In Solid Tumors version 1.1 criteria, the patients who showed a complete response (CR) underwent surgery, and those who achieved a partial response (PR) underwent 4 more cycles of S-1+DOC. Patients who achieved stable disease (SD) or progressive disease (PD) received EC (epirubicin and cyclophosphamide) or HT (trastuzumab and paclitaxel) according to their HER2 status. The primary end point was the pCR rate. **Results:** Ninety-four patients entered the study. After 4 cycles of S-1+DOC, CR was noted in 5 patients, PR in 57, SD in 18, and PD in 3. Of the patients who achieved SD and PD, 12 received EC, and 9 received HT. Among the 83 assessable patients, the pCR rate was 34.9%, and the response rate was 80.7%. The pCR rates were 19.5% in the luminal type group, 53.8% in the luminal HER2 group, 46.1% in the HER2 group, and 50.0% in the triple-negative group. **Conclusion:** The S-1+DOC regimen in this study could be well tolerated and a new candidate neoadjuvant chemotherapy in operable breast cancer patients. It is also expected to be effective even in patients with luminal type disease. However, further randomized control trials are needed to ascertain whether pCR can contribute to favorable outcomes.

Clinical Breast Cancer, Vol. 19, No. 1, 10-6 © 2018 Elsevier Inc. All rights reserved.
Keywords: Complete response, Docetaxel, Neoadjuvant chemotherapy, Operable breast cancer, S-1

Introduction

Neoadjuvant chemotherapy (NAC) has become a standard treatment for breast cancer. The effectiveness of NAC has been documented as follows. Breast cancer patients treated with NAC achieved similar overall survival and disease-free survival rates compared with the patients treated with adjuvant chemotherapy.[1,2] The indication rate for breast-conserving surgery (BCS) increased after NAC,[1,2] and the pathological complete response (pCR) rate was shown to be a surrogate marker of prognosis.[1,3-5] An anthracycline-based followed by taxane regimen provided a superior

[1]Department of Thoracic, Endocrine Surgery and Oncology, Institute of Medical Bio-Sciences, The University of Tokushima Kuramoto-cho, Tokushima, Japan
[2]Department of Surgery, Tokushima Municipal Hospital 2-34, Kitajyosanjima-cho, Tokushima, Japan

Submitted: Apr 25, 2018; Revised: Sep 12, 2018; Accepted: Sep 21, 2018; Epub: Sep 27, 2018

Address for correspondence: Hiroaki Toba, MD, PhD, Department of Thoracic Endocrine Surgery and Oncology, The University of Tokushima, Kuramoto-cho, Tokushima 770-8503, Japan
Fax: +81 88 633 7144; e-mail contact: ht1109@tokushima-u.ac.jp

1526-8209/$ - see frontmatter © 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.clbc.2018.09.008

pCR rate in breast cancer patients.[2,6-8] In addition, sensitivity to NAC can be determined within a short period of time.

Anthracycline-based followed by taxane regimens did not yield satisfactory pCR rates especially for patients with luminal type breast canceer.[8] Anthracycline can cause severe bone marrow suppression and cardiotoxicity. S-1 (Taiho Pharmaceutical Co, Tokyo, Japan) is an oral fluoropyrimidine derivative composed of tegafur, gimeracil, and potassium oxonate. The S-1 monotherapy response rate (RR) among advanced breast cancer patients was 41.7%[9] and that for breast cancer after resistance to anthracycline and taxane was 33.3%.[10] S-1 is thus expected to play a part in the new strategies for breast cancer therapy. S-1 and docetaxel (DOC) combination therapy (S-1+DOC) was reported to have a synergistic antitumor effect in a breast cancer xenograft study, which was suggested to be partly via a significant downregulation of the activity of dihydropyrimidine dehydrogenase, the rate-limiting enzyme in the catabolism of fluorouracil (5-FU).[11,12] S-1+DOC has been established for gastric cancer.[13-15] With the combination of S-1 with low-dose DOC adopted in this study, we expected those synergic effects.

In general, NAC required 24 weeks and prolonged the time to surgery. Therefore, a concern for losing the chance for resection exists. This new combination regimen is expected to achieve high pCR rates in a short period of time. The present study was designed to evaluate the response of S-1+DOC after 4 cycles of administration according to the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST) criteria, and the regimen was switched to EC (epirubicin and cyclophosphamide), or HT (trastuzumab and paclitaxel) according to HER2 status if the response was stable disease (SD) or progressive disease (PD).

Patients and Methods

Study Design and Patient Selection

Eligible patients were 20 to 75 years of age, with histologically confirmed invasive, but noninflammatory primary breast cancer with stage II (tumor size >2 cm) to IIIB disease, and were enrolled in this study if they satisfied the following eligible criteria. They were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1, and were neither pregnant nor nursing. All patients were required to have adequate bone marrow function (absolute neutrophil count $> 2.0 \times 10^3$, platelet count 100×10^3, and hemoglobin level > 9 g/dL) and hepatic and renal functions confirmed in a prestudy examination (ie, bilirubin level < 1.5 times the upper normal limit [UNL], aspartate aminotransferase and or alanine aminotransferase <3 times the UNL, and creatinine clearance ≥60 mL/min). Patients with a history of other cancer within the previous 5 years, heart failure, diabetes mellitus needing continuous insulin therapy, active infection, or mental disease were excluded.

The institutional review board of the Tokushima University Hospital authorized the study. Before entry into the study, each patient was informed about the investigational nature of the study, and written informed consent that was approved by the institutional review board was obtained.

Histologic confirmation of the tumor was performed using core needle biopsy before NAC at the time of breast cancer diagnosis. Estrogen receptor (ER), progesterone receptor (PgR), and HER2 was assessed using immunohistochemistry (IHC). The hormone receptor status was considered positive if >10% of the tumor cells were positively stained for ER and/or PgR. HER2 status was determined using IHC and confirmed with either fluorescent in situ hybridization (FISH) if the IHC result was equivocal (ie, 2+). Fine-needle aspiration of lymph nodes clinically suspected to be diseased was performed. A FISH amplification rate of >2.0 was considered positive.

Treatment Schedule

Eligible patients received DOC 40 mg/m^2 given intravenously (I.V.) on day 1 and oral S-1 on days 1 to 14 every 3 weeks for 4 cycles. The S-1 dose was determined on the basis of the patient's body surface area (BSA) and was administered at 1 of the following doses twice daily: for BSA <1.25 m^2, 40mg; BSA <1.50 m^2, 50 mg; and BSA ≥1.50 m^2, 60 mg. In according with the RECIST criteria, the patients who achieved a complete response (CR) underwent surgery, and the patients who achieved a partial response (PR) underwent 4 additional cycles of S-1+DOC. The patients who had SD or PD received EC (epirubicin 100 mg/m^2 and cyclophosphamide 600 mg/m^2 I.V. on day 1 every 3 weeks for 4 cycles) or HT (trastuzumab 4 mg/kg and paclitaxel 80 mg/m^2 I.V. in week 1, with trastuzumab 2 mg/kg and paclitaxel 80 mg/m^2 I.V. administered in subsequent weeks for 4 cycles or triweekly paclitaxel 175 mg/m^2 on day 1 and trastuzumab) according to their HER2 status (Figure 1).

The dose of S-1 was reduced by 20 mg/d if Grade ≥3 toxicity was observed.

Patients did not receive granulocyte colony-stimulating factor (G-CSF) unless a neutropenic fever occurred. If a patient experienced severe toxicity, a thorough supportive therapy was used in addition to maintain compliance with the S-1 regimen; G-CSF was administered for neutropenic fever, metoclopramide for nausea, lorazepam for anticipatory nausea, alprazolam for depression, and polaprezinc for dysgeusia.

Response Evaluation and Assessment of Adverse Events

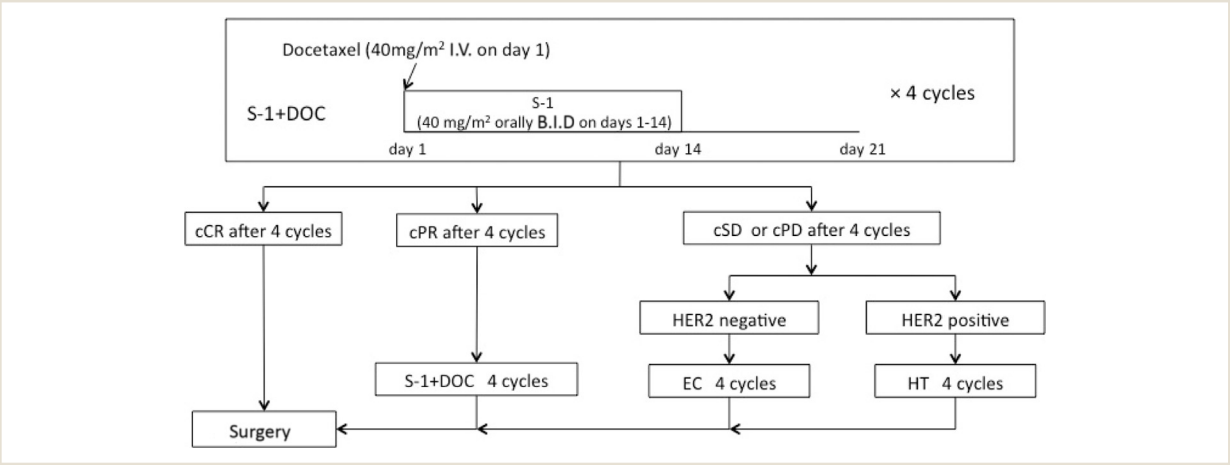
Radiographic evaluations to determine the tumor response were performed after 4 cycles and 8 cycles using computed tomography (CT) scan, magnetic resonance imaging (MRI), mammography, and ultrasonography. According to the RECIST guidelines, CR was defined by the disappearance of all targeted lesions. pCR was defined as the disappearance of the invasive primary tumor and axillary lymph node metastasis determined pathologically (ypT0N0). Quasi-pCR (QpCR) was defined as the absence of invasive tumor or only focal residual tumor cells (ypTisN0).[16] PR was defined as a ≥30% decrease in the sum of the diameters of the target lesions, PD was defined as an increase of ≥20% in the sum of the diameters of the target lesions. Patients who exhibited neither sufficient shrinkage to qualify for a PR or nor a sufficient increase to qualify for PD were considered to have SD.

In accord with the Common Terminology Criteria for Adverse Events version 3.0, toxicity was evaluated after each cycle of chemotherapy.

Surgery and Adjuvant Therapy

Each patient proceeded to surgery after completion of each study schedule. The decision to proceed to mastectomy or BCS was at the

Figure 1 Treatment Schedule



Abbreviations: cCR = clinical complete response; cPD = clinical progressive disease; cPR = clinical partial response; cSD = clinical stable disease; S-1+DOC = S-1 with docetaxel.

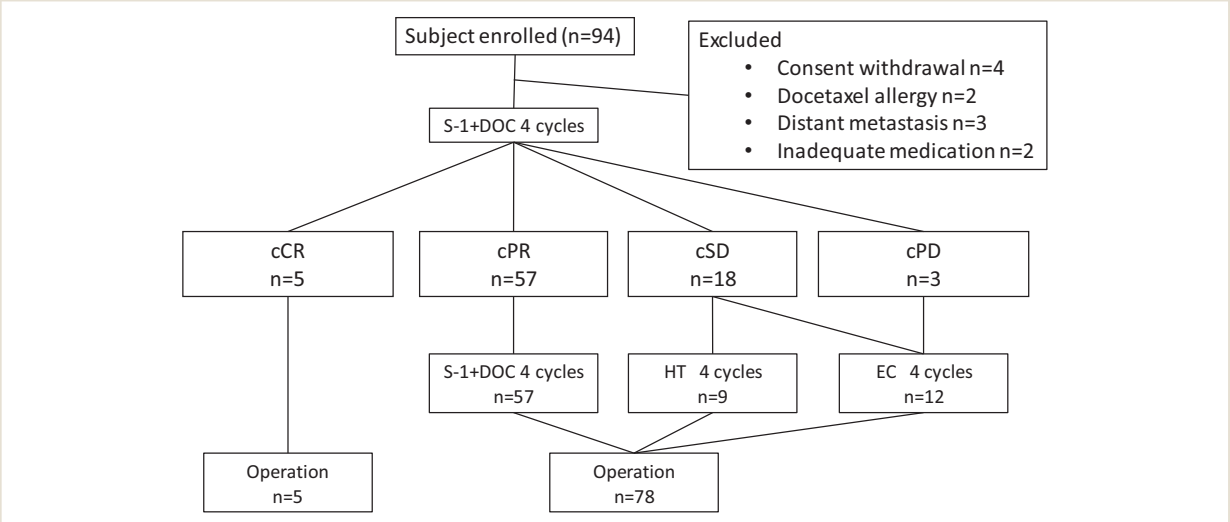
discretion of the surgeon and the patient. All patients with axillary lymph node metastasis before chemotherapy underwent axillary lymph node dissection (ALND). The patients who were clinically node-negative underwent a sentinel lymph node (SLN) biopsy. Clinically N0 patients who showed metastasis in an SLN in pathology were recommended for ALND. All patients who underwent BCS received whole-breast irradiation. Postmastectomy radiotherapy was used in patients with clinical stage III or clinical tumor size ≥5 cm at diagnosis, and in those with pathologic involvement of ≥4 axillary lymph nodes.

Hormone receptor-positive patients underwent adjuvant endocrine therapy for at least 5 years. Patients with HER2-positive ($HER2^{+}$) tumors were advised to receive adjuvant trastuzumab for 1 year.

Assessment End Point

The primary end point was the rate of pCR defined as no microscopic residual viable invasive tumor cells in all resected breast specimens. The secondary end points were the feasibility, RR, BCS rate, and compliance with oral S-1.

Figure 2 Progress of Patients Through the Study



Abbreviations: cCR = clinical complete response; cPD = clinical progressive disease; cPR = clinical partial response; cSD = clinical stable disease; EC = epirubicin and cyclophosphamide; HT = trastuzumab and paclitaxel.

Statistical Analysis

This was a phase II trial with a single-stage design on the basis of binominal distribution, with a 1-sided threshold efficacy rate of 30.0%, which was the lowest pCR rate, an expected pCR rate of 50.0%. When defining an α error of .05 and β error of .10, a total of 55 patients were required to account for dropout cases. Patient characteristics and toxicity are presented as percentages.

Results

Patient Characteristics

From May 2009 to December 2013, 94 patients were enrolled in this study. The full analysis population consisted of 83 patients (Figure 2).

The median age was 53 years (range, 24-75 years), and 38.6% of the patients were premenopausal. The distribution of the 4 breast cancer subtypes was as follows: luminal (ER^+ and/or PgR^+, $HER2^-$), n = 41 (49.4%); luminal HER2 (ER^+ and/or PgR^+, $HER2^+$), n = 13 (15.7%); HER2 (ER^- and/or PgR^-, $HER2^+$), n = 13 (15.7%); and triple-negative (TN; ER^- and/or PgR^-, $HER2^-$): n = 16 (19.3%). The patient characteristics are shown in Table 1.[16]

Efficacy

After 4 cycles of S-1+DOC, 5 patients were clinically judged to have achieved a CR, 57 patients achieved a PR, 18 patients had SD, and 3 patients had PD. The patients continued their respective treatment according to their clinical response (Figure 2).

Table 2 shows overall treatment effect according to pathological response. Twenty-nine patients [34.9%] achieved CR and QpCR,[16] 39 patients [47.0%] achieved PR, 14 patients [16.9%] had SD, and one patient [1.2%] had PD.

Response rate was recognized in 92.3% of luminal HER2, 84.6% of HER2, 87.5% of TN, and 75.6% in luminal type patients (Table 3).[16] Clinical CR (cCR) was seen in 5 patients after 4 courses of the regimen. Shrinkage of the tumor was recognized after 2 courses of the regimen in many patients. Pathological CR (pCR) was recognized in 53.8% of luminal HER2, 46.1% of HER2, 50.0% in TN, and 19.5% in luminal type patients (Table 3). BCS was possible in 65 cases (78.3%).

Twenty-one patients showed SD and PD with this regimen, 12 patients with $HER2^-$ received 4 courses of EC and 9 patients with $HER2^+$ breast cancer received 4 courses of HT. Two pCRs and 9 pathological PRs (pPRs) were recognized in those 12 patients. Nine patients were treated with sequential HT. pCR and QpCR was recognized in 4 patients, and 4 pPRs in 9 patients treated with sequential HT (Table 4).[16] Therefore, the overall RR in this study was 80.7%, and the pCR rate was 34.9%. These RRs and pCR rates were superior compared with the previous study.

Safety

The number of patients who were able to continue taking >80% of their required S-1 dose was 68 (81.9%). The adverse events are summarized in Table 5. The most frequent Grade 3/4 adverse events were leukopenia and neutropenia 39 patients [46.9%], febrile neutropenia 10 patients [12.0%], nail changes 5 patients [6.0%], anorexia 4 patients [4.8%], diarrhea 2 patients [2.4%], and constipation, peripheral neuropathy, and fatigue 1 patient [1.2%]. No treatment-related deaths occurred.

Table 1 Baseline Characteristics of the Study Population (n = 83)

Characteristic	Value
Age, Years	
Average	53.0
Range	24-75
Menopausal Status	
Premenopausal	32 (38.6)
Postmenopausal	51 (61.4)
Subtype	
Luminal[a]	41 (49.4)
Luminal HER2[b]	13 (15.7)
HER2[c]	13 (15.7)
Triple-negative[d]	16 (19.3)
Clinical Tumor Stage	
T2	65 (60.6)
T3	8 (9.6)
T4	10 (12.0)
Clinical Nodal Status	
N0	17 (20.5)
N1	59(71.0)
N2	7 (8.4)
Histology	
Invasive ductal carcinoma	76 (91.6)
Invasive lobular carcinoma	2 (2.4)
Special types	5 (6.0)

Data are n (%) except where otherwise noted.
Abbreviations: ER = estrogen receptor; PgR = progesterone receptor.
[a]Luminal = ER^+ and/or PgR^+, $HER2^-$.
[b]Luminal HER2 = ER^+ and/or PgR^+, $HER2^+$.
[c]HER2 = ER^- and/or PgR^-, $HER2^+$.
[d]Triple-negative = ER^- and/or PgR^-, $HER2^-$.

Discussion

Docetaxel and 5-FU have been shown to be synergistic in vivo and in vitro, which constitutes the rationale for combining S-1 and DOC.[17] A phase I study was carried out to determine the maximum tolerated dose and the recommended dose of DOC with a fixed dose of S-1. We carried out the phase I study in Japanese gastric cancer patients.[13]

The pCR rate was 34.9% in this population. In other NAC studies, the pCR rates ware 14% to 35.4%.[1-8,18-21] The pCR rate for the present group of luminal type (ER^+ and/or PR^+, $HER2^-$) patients was 19.5%. Other studies reported lower pCR rates for the

Table 2 Pathological Response (n) = 83

Response	n	%
CR	18	34.9
QpCR	11	
PR	39	47.0
SD	14	16.9
PD	1	1.2

Abbreviation: QpCR = quasi-pathological CR (absence of invasive tumor or only focal residual tumor cells).[16]

Table 3 Pathological Response Evaluation Criteria In Solid Tumors Response

Subtype	CR + QpCR	PR	SD	PD	pCR rate	RR
Luminal[a]	8	23	10	0	19.5	75.6
Luminal HER2[b]	7	5	1	0	53.8	92.3
HER2[c]	6	5	2	0	46.1	84.6
Triple-Negative[d]	8	6	1	2	47.0	87.5

Abbreviations: ER = estrogen receptor; pCR = pathological CR; PgR = progesterone receptor; QpCR = quasi-pathological CR (absence of invasive tumor or only focal residual tumor cells)[16]; RR = response rate.
[a]Luminal = ER^+ and/or PgR^+, $HER2^-$.
[b]Luminal HER2 = ER^+ and/or PgR^+, $HER2^+$.
[c]HER2 = ER^- and/or PgR^-, $HER2^+$.
[d]Triple-negative = ER^- and/or PgR^-, $HER2^-$.

luminal type (0%-16.2%).[3,4,20] von Minckwitz et al analyzed 6377 operable patients receiving neoadjuvant anthracycline—taxane-based chemotherapy using data from 7 randomized control trials (RCTs), in which T status was almost identical to ours, and showed that of 6377 patients, 1450 achieved a pCR (22.7%), and for 1849 patients of the luminal type 145 achieved a pCR (7.8%.[20] As a result, our pCR rates were higher compared with theirs although it is difficult to compare simply because our study had a small sample size enrolled, and it was a phase II trial. However, we believe that our regimen is expected to be effective NAC in terms of achieving good pCR. Anthracycline and taxane-based therapy, which is a standard regimen, is known to have low efficacy against breast cancer of the luminal type. Moreover, this regimen with S-1 and low-dose DOC showed patients to achieve a cCR in a very short time period, compared with the previous sequential regimens.[3-8,18-20] Synergic effects of S-1 can be estimated because of the lower dose of DOC, which realized a higher pCR rate compared with the average doses of taxanes in the previous studies. The objective RR was 80.7% and pCR rate was 53.8% for the luminal HER2 type, 46.1% for the HER2 type, and 50.0% for the TN type. Twenty-one patients showed SD and PD in this regimen and were salvaged with a sequential regimen. Twelve patients of $HER2^-$ subtype received 4 courses of EC and 9 patients who were $HER2^+$ received 4 courses of HT. Two pCRs and 9 pPRs were recognized in those 12 patients. Nine patients were treated with sequential HT. pCR and QpCR was recognized in 4 patients; 4 pPRs in 9 patients treated with sequential HT (Table 4). Only 3 of 83 patients could not achieve efficacy in this study (1 patient with PD and 2 with SD). Eighty of 83 patients (96.4%) obtained clinical benefit from this study. Response rates were superior compared with to those in the previous study.[20]

Efficacy of S-1 against luminal type breast cancer has attracted attention recently. The pCR rate was 19.5% in the patients with the luminal type who were treated with this regimen. Although Ki-67

Table 4 Items of Treatment Course

Regimen	n	Subtype		Pathological Response
S-1+DOC 4 Cycles	5	Luminal[a]	1	SD 1
		Luminal HER2[b]	0	–
		HER2[c]	2	CR + QpCR 1, PR 1
		TN[d]	2	CR + QpCR 2
S-1+DOC 8 Cycles	57	Luminal[a]	33	CR + QpCR 8, PR 17, SD 9
		Luminal HER2[b]	10	CR + QpCR 5, PR 5
		HER2[c]	5	CR + QpCR 3, PR 1, SD 1
		TN[d]	9	CR + QpCR 4, PR 3, SD 1
S-1+DOC 4 Cycles Followed by EC 4 Cycles	12	Luminal[a]	6	PR 6
		Luminal HER2[b]	–	–
		HER2[c]	–	–
		TN[d]	6	CR + QpCR 2, PR 3, PD 1
S-1+DOC 4 cycles Followed by HT 4 cycles	9	Luminal[a]	–	–
		Luminal HER2[b]	3	CR + QpCR 2, SD 1
		HER2[c]	6	CR + QpCR 2, PR 4
		TN[d]	–	–

Abbreviations: EC = epirubicin and cyclophosphamide; ER = estrogen receptor; HT = epirubicin and cyclophosphamide; PgR = progesterone receptor; QpCR = quasi-pathological CR (absence of invasive tumor or only focal residual tumor cells)[16]; RR = response rate; S-1+DOC = S-1 (Taiho Pharmaceutical Co, Tokyo, Japan) with docetaxel; TN = triple-negative.
[a]Luminal = ER^+ and/or PgR^+, $HER2^-$.
[b]Luminal HER2 = ER^+ and/or PgR^+, $HER2^+$.
[c]HER2 = ER^- and/or PgR^-, $HER2^+$.
[d]TN = ER^- and/or PgR^-, $HER2^-$.

Table 5 Adverse Events

Event	Grade 1/2, n	Grade 3/4, n	Grade 3/4 (%)
Alopecia	83	–	–
Febrile Neutropenia	–	10	12.0
Nail Changes	60	5	6.0
Hand-Foot Syndrome	45	0	0
Dysgeusia	52	–	–
Anorexia	50	4	4.8
Vomiting	14	0	0
Constipation	33	1	1.2
Diarrhea	35	2	2.4
Mucositis	30	0	0
Pleural or Pericardial Effusion	2	0	0
Edema: Limb	8	0	0
Peripheral Neuropathy	35	1	1.2
Fatigue and Asthenia	30	1	1.2
Leukopenia	26	39	46.9
Neutropenia	11	39	46.9
Anemia	13	1	1.2
Liver Dysfunction	3	0	0

evaluation was not performed in all luminal type patients in this study, pCR did not depend on the Ki-67 value in calculations using data from several patients who had Ki-67 evaluated in this study. Of 8 pCR cases of luminal type, 3 (32.5%) cases were luminal A, and 5 (62.5%) were luminal B. This result would realize the effective chemotherapy even in luminal A type breast cancer, in which NAC was not performed, with remarkable efficacy.[19] The SELECT BC (SELection of Effective ChemoTherapy for Breast Cancer) trial showed that S-1 is not inferior to taxane as a first-line treatment for metastatic breast cancer. In the subgroup analyses, S-1 was effective against hormone receptor-positive tumors.[21] Thus, oral S−1-based therapy compares favorably with the standard regimen, especially for the luminal type cancer.

Two patients with TN type tumor showed pathological PD. One of them was spindle-cell carcinoma. The other patient achieved a pPR after the sequential EC treatment. Among the 5 patients who underwent surgery after 4 cycles of S-1+DOC, pCR was achieved in 3 patients (2 TN, 1 HER2 type), pPR was achieved in 1 patient (HER2 type), and pathological SD was observed in 1 patient (luminal type). In TN or HER2 type, 24 patients underwent 8 cycles of S-1+DOC. Twelve of them achieved pCR. Some research groups have indicated that the pCR after NAC can be considered a prognostic factor in advanced TN type and HER2 type cancer.[3,4,20]

One patient with luminal type cancer achieved pathological SD according to resected specimen examination. In our study, the determination of cCR was on the basis of MRI, CT scan, mammography, and ultrasonography, but several studies showed that MRI measurement was inaccurate for luminal type cancer.[22-24] The determination of cCRs should be interpreted with caution according to the subtype. Moon et al described their use of S-1+DOC after AC (doxorubicin with cyclophosphamide) as NAC.[25] In that study, the patients received AC every 3 weeks for 4 cycles followed by S-1 (30 mg/m^2 orally twice per day [B.I.D.] on days 1-14) and DOC (75 mg/m^2 I.V. on day 1) every 3 weeks for 4 cycles. The pCR rate was 22.5% and the clinical RR was 67.4%; 85.4% of the patients completed 8 cycles of therapy. There was a single treatment-related mortality from severe neutropenia. Gastrointestinal discomfort led to a dose reduction of S-1 in 45.8% of the patients.[25] In our present study, DOC (40 mg/m^{2}I.V. on day 1) and S-1 (40 mg/m^2 orally B.I.D. on days 1-14) were used in accord with a phase I study of Japanese patients with recurrent gastric cancer.[14] Our results are better when they are recalculated without HER2 cases (pCR rate of 28.0% and RR rate of 77.2%).

Because of the S-1 is an oral medicine that is taken by the patient by themselves at home, it is particularly important that the patients maintain compliance with the drug regimen. There are few reports about compliance regarding oral medications for breast cancer. However, this regimen is one of the standard treatment regimens for gastric cancer treatment in Japan. In the treatment of gastric cancer, it was reported that the second-generation histamine H2 receptor antagonist lafutidine might be useful not only for preventing gastrointestinal toxicities during adjuvant chemotherapy, but also for improving compliance with a regimen of oral 5-FU anticancer drugs.[26] Supportive therapy was provided for almost all patients, who revealed adverse events in this study. Sixty-eight patients (81.9%) took S-1 at more than 80% of the required dose. Some patients stopped taking S-1 before the 14-day point was reached, because of Grade 1/2 gastrointestinal symptoms or fatigue. Although S-1 treatment can provide a superior quality of life,[21] its use requires close supervision because it is an oral medicine. It will be important to identify predictive factors for S-1 effects and adverse events, and to provide regular examinations as a back-up. There was no mortality in our study.

Limitations

Because this study was phase II, the patients' long-term outcome was not described. von Minckwitz et al also addressed the

association with the prognosis and pCR in intrinsic subtypes, and showed that pCR is a suitable surrogate end point for patients with luminal B/HER2$^-$ disease, but not for those with luminal A disease.[20] To address whether pCR will contribute to a good prognosis in our neoadjuvant setting, further RCTs are needed. Trastuzumab combined therapy is recommended for HER2$^+$ breast cancer. Clinical SD or clinical PD HER2$^+$ patients changed to HT therapy after 4 cycles of S-1+DOC. However, 15 of clinical PR HER2$^+$ patients continued S-1+DOC without trastuzumab. These patients might expect improved RRs with trastuzumab combined therapy. Further studies are needed. The patients who received surgery after 4 cycles S-1+DOC should be verified. The sample size was small and the judgement of cCR should be reconsidered. There is a potential that NAC treatment time can be shortened. These patients need adequate follow-up.

Conclusion

The S-1+DOC regimen in this present study could be well tolerated and a new candidate NAC in operable breast cancer patients. It is also expected to be effective even in patients with luminal type disease. However, further RCTs will be needed to ascertain whether pCR can contribute to favorable outcomes.

Clinical Practice Points

- To improve the pCR rate, we devised a new NAC treatment.
- Efficacy and safety of the oral fluoropyrimidine derivative S-1 combined with low-dose DOC were evaluated.
- Patients were treated with S-1+DOC for 4 cycles.
- In accord with the RECIST criteria, the patients who showed a CR underwent surgery, and those who achieved a PR underwent 4 more cycles of S-1+DOC.
- Patients with SD or PD received EC or HT according to their HER2 status.
- The primary end point was the pCR rate.
- Ninety-four patients entered the study.
- After 4 cycles of S-1+DOC, CR was noted in 5 patients, PR in 57, SD in 18, and PD in 3. Among the 83 assessable patients, the pCR rate was 34.9%, and the RR was 80.7%. The pCR rates were 19.5% for patients with the luminal type breast cancer.
- Patients who received S-1+DOC showed a previous response to a previous protocol with anthracycline with cyclophosphamide followed by taxane treatment.
- Our results suggest that S-1+DOC was expected to be an effective chemotherapy for luminal-type breast cancer.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local- regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997; 15: 2483-93.
2. Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2003; 21:4165-74.
3. Wang-Lopez Q, Chalabi N, Abrial C, et al. Can pathologic complete response (pCR) be used as a surrogate marker of survival after neoadjuvant therapy for breast cancer? *Crit Rev Oncol Hematol* 2015; 95:88-104.
4. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014; 384:164-72.
5. Prat A, Fan C, Fernández A, et al. Response and survival of breast cancer intrinsic subtypes following multi-agent neoadjuvant chemotherapy. *BMC Med* 2015; 13:303.
6. von Minckwitz G, Raab G, Caputo A, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPAR-DUO study of the German Breast Group. *J Clin Oncol* 2005; 23:2676-85.
7. Smith IC, Heys SD, Hutcheon AW, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. *J Clin Oncol* 2002; 20: 1456-66.
8. Houssami N, Macaskill P, von Minckwitz G, et al. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. *Eur J Cancer* 2012; 48:3342-54.
9. Saek T, Takashima S, Sano M, et al. A phase II study of S-1 in patients with metastatic breast cancer–a Japanese trial by the S-1 Cooperative Study Group, Breast Cancer Working Group. *Breast Cancer* 2004; 11:194-202.
10. Yuan P, Di LJ, Liu W, et al. Phase II multi-center clinical study on using S-1 to treat advanced breast cancer after resistance to anthracycline and taxane drugs in Chinese patients. *Int J Clin Exp Med* 2015; 8:3072-9.
11. Suto A, Kubota T, Fukushima M, et al. Antitumor effect of combination of S-1 and docetaxel on the human breast cancer xenograft transplanted into SCID mice. *Oncol Rep* 2006; 13:1517-22.
12. Wada Y, Yoshida K, Suzuki T, et al. Synergistic effects of docetaxel and S-1 by modulating the expression of metabolic enzymes of 5-fluorouracil in human gastric cancer cell lines. *Int J Cancer* 2006; 119:783-91.
13. Yoshida K, Hirabayashi N, Takiyama W, et al. Phase I study of combination therapy with S-1 and docetaxel (TXT) for advanced or recurrent gastric cancer. *Anticancer Res* 2004; 24:1843-51.
14. Yoshida K, Toge T. Combination chemotherapy of TS-1 and docetaxel on advanced and recurrent gastric cancer [in Japanese]. *Gan To Kagaku Ryoho* 2004; 31:1982-6.
15. Yamada K, Sugiyama Y, Seino K, et al. A case of a nonresected gastric cancer with peritoneal dissemination maintained on TS-1 and docetaxel combination chemotherapy with good QOL [in Japanese]. *Gan To Kagaku Ryoho* 2005; 32: 223-6.
16. Namikawa T, Munekage E, Maeda H, et al. Feasibility study of supportive care using lafutidine, a histamine H2 receptor antagonist, to prevent gastrointestinal toxicity during chemotherapy for gastric cancer. *Anticancer Res* 2014; 34:7297-301.
17. Takeda Y, Yoshizaki I, Nonaka Y, Yanagie H, Matsuzawa A, Eriguchi M. Docetaxel alone or orally combined with 5-fluorouracil and its derivatives: effects on mouse mammary tumor cell line MM2 in vitro and in vivo. *Anticancer Drugs* 2001; 12:691-8.
18. A L-Tweigeri T, AlSayed A, Alawadi S, et al. A multicenter prospective phase II trial of neoadjuvant epirubicin, cyclophosphamide, and 5-fluorouracil (FEC100) followed by cisplatin-docetaxel with or without trastuzumab in locally advanced breast cancer. *Cancer Chemother Pharmacol* 2016; 77:147-53.
19. Nakatsukasa K, Koyama H, Oouchi Y, et al. Docetaxel and cyclophosphamide as neoadjuvant chemotherapy in HER2-negative primary breast cancer. *Breast Cancer* 2017; 24:63-8.
20. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012; 30:1796-804.
21. Takashima T, Mukai H, Hara F, et al. Taxanes versus S-1 as the first-line chemotherapy for metastatic breast cancer (SELECT BC): an open-label, non-inferiority, randomised phase 3 trial. *Lancet Oncol* 2016; 17:90-8.
22. Schaefgen B, Mati M, Sinn HP, et al. Can routine imaging after neoadjuvant chemotherapy in breast cancer predict pathologic complete response? *Ann Surg Oncol* 2016; 23:789-95.
23. Semiglazov V. RECIST for response (clinical and imaging) in neoadjuvant clinical trials in operable breast cancer. *J Natl Cancer Inst Monogr* 2015; 2015:21-3.
24. Charehbili A, Wasser MN, Smit VT, et al. Accuracy of MRI for treatment response assessment after taxane- and anthracycline-based neoadjuvant chemotherapy in HER2-negative breast cancer. *Eur J Surg Oncol* 2014; 40: 1216-21.
25. Moon YW, Lee S, Park BW, et al. S-1 combined with docetaxel following doxorubicin plus cyclophosphamide as neoadjuvant therapy in breast cancer: phase II trial. *BMC Cancer* 2013; 13:583.
26. Toi M, Nakamura S, Kuroi K, et al. Phase II study of preoperative sequential FEC and docetaxel predicts of pathological response and disease free survival. *Breast Cancer Res Treat* 2008; 110:531-9.