Ann. Cancer Res. Ther. Vol. 30, No. 1, pp. 38-44, 2022

Original papers

Longitudinal efficacy and safety of capecitabine and cyclophosphamide as early-line treatment in patients with metastatic breast cancer: A prospective cohort study by the Kyushu Breast Cancer Study Group, Japan.

Kohjiro Mashino[1)], Maki Tanaka[2)], Miki Yamaguchi[2)], Reiki Nishimura[3)], Yutaka Yamamoto[4)], Hiroaki Ueo[5)], Toshihiro Tanaka[6)], Kenichiro Koga[7)], Tomoyuki Yoshiyama[8)], Shoshu Mitsuyama[7)], Kazuo Tamura[6)], and the Kyushu Breast Cancer Study Group

[1)] *Department of Breast Surgery, Oita Prefectural Hospital, Oita, Japan*
[2)] *Department of Breast Surgery, JCHO Kurume General Hospital, Kurume, Japan*
[3)] *Department of Breast Oncology, Kumamoto Shinto General Hospital, Kumamoto, Japan*
[4)] *Department of Breast and Endocrine Surgery, Kumamoto University Hospital, Kumamoto, Japan*
[5)] *Department of Surgery, Ueo Breast Cancer Hospital, Oita, Japan*
[6)] *Division of Oncology, Hematology, and Infectious Diseases, Department of Internal Medicine, Fukuoka University, Fukuoka, Japan*
[7)] *Department of Surgery, Kitakyushu Municipal Medical Center, Kitakyushu, Japan*
[8)] *Department of Breast Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan*

Abstract

Introduction: Oral combination chemotherapy using capecitabine and cyclophosphamide (XC) has demonstrated synergistic antitumor activity in preclinical studies. We investigated the efficacy and safety of early-linen XC therapy use in patients with metastatic breast cancer (MBC).

Methods: In this prospective cohort study conducted at 10 site in Kyushu, Japan, patients with human epidermal growth factor receptor 2 (HER2)-negative MBC, regardless of the history of previous treatment, were enrolled. XC therapy was administered at the recommended dose on a three-week schedule for at least six courses unless disease progression and unacceptable toxicities occurred. The primary endpoint was response rate (RR), and the secondary endpoints were progression-free survival (PFS), overall survival (OS), and adverse events.

Results: Of the 83 patients enrolled, 71 (median age, 60 years [range, 34–86 years]) fulfilled the inclusion criteria and were analyzed. A total of 45 (63%) patients did not previously receive chemotherapy for metastatic disease, 10 (14%) received one chemotherapy regimen. The median number of cycles of XC was eight (range, 1–45), and the RR was 28%. Median PFS was 7.6 months (95% confidence interval [CI]: 5.7–9.5 months), and median OS was 26.4 months (95% CI: 13.9–38.9 months). The most frequent grade 3–4 adverse events were leukopenia (n = 20) and neutropenia (n = 15).

Conclusions: In clinical practice, XC therapy exhibited efficacy and manageable tolerability in Japanese women with MBC in early-line use. (ID: UMIN000044444)

Keywords: capecitabine, cyclophosphamide, metastatic breast cancer, prospective cohort study

(Received February 28, 2022; Accepted April 4, 2022)

Introduction

Metastatic breast cancer (MBC) remains incurable; as such, the goals of therapy are to prolong survival, alleviate symptoms, and optimize quality of life (QoL). Anthracycline- or taxane-containing regimens have often been chosen as a first-line therapy for human epidermal growth factor receptor 2 (HER2)-negative MBC. Current guidelines suggest the use of an agent for first-line therapy to optimize the treatment length and QoL[1)]. However, with the long-term use of these drugs, virtually all patients experience adverse events including peripheral neuropathy, hair loss, and cardiotoxicity. Based on these guidelines, agents with reduced toxicity—but with comparable efficacy to that of anthracyclines and taxanes—could be a therapeutic option as a first-line therapy in such patients. In fact, a recent clinical study conducted in Japan demonstrated that the oral 5-fluorouracil (5-FU) derivative S-1 is non-inferior to taxane in terms of overall survival (OS) and QoL as first-line chemotherapy for patients of MBC[2)].

Corresponding author: Kohjiro Mashino, MD, PhD., Department of Breast Surgery, Oita Prefectural Hospital, 2-8-1, Bunyo, Oita City, Oita 870-8511, Japan. E-mail: k-mashino@oitapref-hosp.jp

Capecitabine is an oral active agent that is converted to 5-FU in a three-step enzymatic process and delivered selectively to the neoplastic tissue[3]. After gastrointestinal absorption, capecitabine is hydrolyzed in the liver; deaminated by cytidine deaminase, an enzyme located principally in the hepatic and neoplastic tissue; and catalyzed by thymidine phosphorylase. Because thymidine phosphorylase activity is higher in neoplastic tissues than in normal tissues, 5-FU is preferentially generated in the neoplastic tissues. Previous clinical studies have shown that capecitabine monotherapy is an active first-line therapy for patients with anthracycline- and taxane-refractory MBC[4, 5].

In xenograft and mammary tumor models, the administration of taxanes or cyclophosphamide was shown to upregulate the levels of thymidine phosphorylase in neoplastic tissues, and combination therapy using these agents with capecitabine demonstrated synergistic antitumor effects without significantly potentiating toxicity[6, 7]. In humans, the efficacy of the combination of capecitabine and docetaxel was clinically demonstrated in a phase III study, which showed that the aforementioned therapy resulted in significantly superior time to progression and OS, with a manageable toxicity profile compared with that of docetaxel monotherapy[8]oncologists are frequently faced with the challenge of treating patients whose disease has progressed during or following anthracycline therapy or who are ineligible for further anthracycline therapy. Many of these women remain candidates for cytotoxic chemotherapy, and several treatment options exist. Until recently, the taxanes, docetaxel in particular, were widely regarded as the most effective therapy for these patients, based on a survival advantage observed with docetaxel. However, a recent phase III study demonstrated that the addition of capecitabine to docetaxel results in superior overall survival (with a 3-month improvement in median survival.

Oral administration of antineoplastic agents is convenient, leading to enabling outpatient therapy much easily, which is believed to improve QoL compared to hospital-based therapy, especially in patients with advanced cancers. Both capecitabine and cyclophosphamide are active therapeutic agents for breast cancer and can be administered orally. Harvey et al. demonstrated the efficacy and feasibility of combined capecitabine and cyclophosphamide (XC) therapy in a randomized study in comparison with the capecitabine monotherapy[9]. We conducted phase I study of the combination therapy in patients with MBC, and the recommended dose of these agents was established[10]. The excellent antitumor effects and favorable toxicity profiles of XC therapy were revealed in a prospective phase II study[11]. This study was undertaken to prospectively evaluate the clinical efficacy of XC therapy as well as its adverse reactions in clinical practice.

Methods

Patients

Female patients with histologically-confirmed HER2-negative MBC including those with unresectable advanced disease, aged ≥20 years, with no history of combination chemotherapy with 5'-deoxy-5-fluorocytidine and cyclophosphamide other than perioperative chemotherapy which was given before at least 12 months since the last administration, with Eastern Cooperative Oncology Group performance status (ECOG-PS) 0 to 3, with measurable lesion(s) based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, with at least 3 months of life expectancy, and with adequate bone marrow, liver, renal, and lung function were included in the study. Premenopausal women with hypersensitivity to pyrimidine fluoride drugs or cyclophosphamide, systemic infection, uncontrolled pleural effusion or ascites, pericardial effusion, symptomatic brain tumor, serious complications, active concomitant malignancy, or history of organ transplantation and those who are pregnant including those with possible pregnancy were excluded. Patients who were considered to be ineligible by the investigator were also excluded.

Study design

This prospective, single-arm, multicenter cohort study was conducted at 10 sites in Japan. The study protocol and all amendments were approved by the local ethics committees or at the institutional review board at each participating study site. This trial was conducted in accordance with the Japanese Guidelines for Clinical Research of the Ministry of Health, Labor and Welfare, and the Declaration of Helsinki as well as other regulatory requirements. All participants provided written informed consent before enrolled into the study. This investigator-initiated clinical trial was supported by nonprofit organization the Clinical Hematology-Oncology Treatment Study Group (CHOT-SG).

The doses of capecitabine and cyclophosphamide were determined according to an earlier phase I trial[10]. A capecitabine dose of 1,657 mg/m^2/day and a cyclophosphamide dose of 65 mg/m^2/day were given orally twice daily from days 1 to 14 and one week rest. The treatment was continued for at least six cycles at a every three-week cycle or until disease progression or toxicity or significant complications as described below. Treatment beyond six cycles was permitted at the discretion of the treating physician.

The therapy was withheld if significant toxicity occurred, and the treatment was resumed once the toxicity had resolved as dose adjustment was taken place. The treatment modification measures were as follows. The next cycle of treatment was initiated if the following con-

ditions were met: neutrophil count ≥1.5×10^9/L, platelet count ≥75×10^9/L, hemoglobin ≥8 g/dL, serum creatinine ≤1.5 times the upper limit of normal, serum total bilirubin ≤1.5 times the upper limit of normal, and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels ≤2.5 times the upper limit of normal. The treatment was interrupted if patients developed an adverse event classified as grade 2, 3, or 4 according to the National Cancer Institute Common Toxicity Criteria. Treatment was interrupted at the first occurrence of grade 2 toxicity and then resumed at the original dose once the toxicity has resolved to grade 0–1. If the same grade 2 toxicity subsequently occurred, then treatment was discontinued and the dose was reduced by 25%. If grade 3 or 4 toxicity occurred, then treatment was interrupted, and the dose was reduced by 25% or 50%, respectively. At the third appearance of grade 2 toxicity or the second appearance of grade 3 toxicity, the treatment was interrupted until the toxicity resolved to grade 0–1, and treatment was continued at 50% of the original dose. Treatment was discontinued at the third occurrence of grade 3 toxicity or the second appearance of grade 4 toxicity, and the patient was withdrawn from the study. The treatment was maintained as long as treatment response was persisted and toxicity was acceptable.

Study assessments

Tumor size was measured according to the RECIST guideline at baseline, and tumor response was assessed after every two cycles of XC. Hematological and non-hematological toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

The primary aim of the present study was to objectively determine the RR, i.e., complete response (CR) + partial response (PR). Secondary objectives were to estimate the progression-free survival (PFS) and OS and to determine the safety of this regimen. The PFS and OS were calculated and compared using the Kaplan-Meier method and log-rank test. PFS was defined as the interval from the time of assignment to this study until progression of the disease or death from any cause. OS was measured from the time of inclusion into this study until death from any cause. Survivors who did not experience disease progression were censored at the last date of contact. All eligible patients who received at least one dose of XC were included in the intention-to-treat analysis of efficacy and safety.

Statistical analysis

The threshold response rate was set to 25% in consideration of the response rate of capecitabine alone in the first-line therapeutic effect on MBC, and the expected response rate was set to 40% in consideration of the response rate of taxane-based monotherapy[8, 9].

The required sample size was estimated based on a threshold RR of 25% and an expected RR of 40%, 80% power, and an alpha value of 0.1 (one-sided) using the binomial test. Given 10% of ineligible patients, the target sample size was determined to be at least 70 patients. We used the Kaplan–Meier method to estimate survival curves to calculate 95% CIs for survival rates. Statistical analyses were performed using BellCurve version 3.20 (Social Survey Research Information Co., Ltd, Tokyo, Japan) for Excel (Microsoft Corporation, Redmond, WA, USA).

Results

Patients

A total of 83 patients were enrolled in this study between November 2009 and February 2012. Of them, 12 were excluded because they did not meet the inclusion criteria; thus, 71 patients were eligible for this study. The demographic and baseline characteristics of the patients are summarized in Table 1. The median age was 60 years (range, 34–86 years), and all patients had an ECOG-PS of 0 or 1. A total of 55 (77%) patients had estrogen receptor (ER)-positive MBC, 41 (58%) had progesterone receptor-positive MBC, and 11 (16%) did not have both receptors.

Table1 Patient demographics and baseline characteristics

Characteristics	No. of patients (%)
Eligible patients	71 (100)
Age, years	
Median (Range)	60 (34–86)
≤49	12 (17)
50–64	35 (49)
≥65	24 (34)
ER status	
positive	55 (77)
negative	16 (23)
PR status	
positive	41 (58)
negative	30 (42)
Metastatic sites	
Visceral metastases	52 (73)
Liver	38 (54)
Lung	27 (38)
Soft tissue	30 (42)
Bone	43 (61)
Others	13 (18)
Number of metastatic sites	
1	13 (18)
2	25 (35)
≥3	33 (46)
Prior adjuvant chemothrapy	44 (62)
Anthracyclin or/and Taxane containing	28 (39)
FU containing	9 (13)
Others	2 (3)
Prior chemotherapy for metastatic disease	
0	45 (63)
1	10 (14)
≥2	16 (23)

Table2 Response to the treatment by the number of prior regimens, by the ER status, and by the patients' age.

		Number of patients	Over all response (%)	Clinical Benefit (%)	Best response					
					CR	PR	SD≥ 6months	SD< 6months	PD	NA
Prior chemotherapy for MBC	0	45	16 (36)	27 (60)	3 (7)	13 (29)	11 (24)	7 (16)	7 (16)	4 (9)
	1	10	1 (10)	7 (70)	0 (0)	1 (10)	6 (60)	1 (10)	2 (20)	0 (0)
	2≤	16	3 (19)	9 (56)	0 (0)	3 (19)	6 (38)	3 (19)	2 (13)	2 (13)
ER status	positive	55	13 (24)	34 (62)	2 (4)	11 (20)	21 (38)	8 (15)	7 (13)	6 (11)
	negative	16	7 (44)	9 (56)	1 (6)	6 (38)	2 (13)	3 (19)	4 (25)	0 (0)
Age	≤64	47	16 (34)	29 (62)	3 (6)	13 (28)	13 (28)	6 (13)	7 (15)	5 (10)
	65≤	24	4 (17)	14 (58)	0 (0)	4 (17)	10 (41)	5 (21)	4 (16)	1 (4)
Total		71	20 (28)	43 (61)	3 (4)	17 (24)	23 (32)	11 (15)	11 (15)	6 (8)

Table3 Clinical benefit rate of the treatment by the metastatic site.

Metastatic site of CR, PR or SD (IR/SD)≥6months /number of assessable patients (%)							
Prior chemothrapy for MBC	Metastatic site						
	Liver	Bone	Lung (visceral)	Lung (pleural)	Skin	Lymph node	Contralateral breast
0	9/18 (50)	21/25 (84)	11/16 (69)	4/5 (80)	2/3 (67)	14/22 (64)	N.A
1or2	15/19 (79)	15/17 (88)	10/11 (91)	N.A	1/2 (50)	5/6 (83)	1/1 (100)
Total	24/37 (65)	36/42 (86)	21/27 (78)	4/5 (80)	3/5 (60)	19/28 (68)	1/1 (100)

N.A: not assessable.

Lung or liver metastasis was present in 27 (38%) and 38 (54%) patients, respectively. Among the 71 patients treated in this study, 44 (62%) had previously undergone adjuvant chemotherapy. A total of 45 (63%) patients did not previously receive chemotherapy for metastatic disease, 10 (14%) received one chemotherapy regimen, and 15 (21%) received two chemotherapy regimens.

The median number of XC therapy cycles was eight (range, 1–45). The reasons of discontinuing the treatment beyond 6 cycles are progression of disease (32%), severe diarrhea (1%), bone marrow suppression (1%), severe weight loss (1%), infection (1%), and pulmonary embolism (1%).

Efficacy analysis

The best responses to the treatment protocol are summarized in Table 2. Objective CR and PR were observed in 20 of the 71 patients in the intention-to-treat population, resulting in an overall RR of 28%. Thirty-four (48%) additional women had stable disease (SD), and 23 had SD for ≥ 6 months, corresponding to a clinical benefit response (CBR [CR +PR + SD ≥ 6 months]) rate of 61%. For patients without prior chemotherapy for metastatic lesions, the response rate was 36% and CBR was 60%. Table 2 summarizes the efficacy by treatment line, ER expression, and age. Over all RR in the first line therapy is 36%, while that of beyond the second line therapy is 19%. The analysis of ER expression revealed that the overall RR was 24% in the ER-positive group and 44% in the ER-negative group, respectively. Over all RR of the treatment in the elderly aged 65 and over was 17%, and that in the aged 64 and under was 34%. CBR was 58% and 62%, respectively.

Table 3 shows the CBR rates according to the metastatic site. The clinical benefits to receiving this treatment were observed in 65% of patients with liver, 68% of those with lymph node, and 78% of those with lung metastases.

The median duration of follow-up was 16.1 months. Median PFS based on the Kaplan-Meier estimate was 7.6 months (95% CI: 5.7–9.5 months [range, 1–23 months]), and median OS was 26.4 months (95% CI: 13.9–38.9 months [range, 1–60 months]).

Safety analysis

The different adverse events of this treatment are summarized in Table 4. Of the 71 patients, grade 3 leukopenia was observed in 20 (28%), neutropenia was observed in 14 (19%), anemia was observed in two (3%), and thrombocytopenia was observed in two (3%) patients. One patient died of pulmonary embolism after receiving one cycle of treatment. This patient had a large tumor burden, with metastases to the liver, lung, skin, and lymph nodes, which were resistant to endocrine therapy. There were grade 1/2 non-hematological toxicities. The ALT and AST levels increased to grade 3 in two (3%) patients and one (1%) patient, respectively. Hand-foot syndrome was observed in 24 (34%) patients, although grade 3 was observed in only one (1%) patient. Twenty-four (34%) patients were discontinued before 6 cycles of treatment. Fifteen (21%) patients were discontinued due to disease progression. Two patients were discontinued due to changes in their own intentions, and the other two were discontinued due to the protocol regulations. Other

Table4 Treatment-related adverse events.

	number of patients (percent) N=71					
Adverseevent (AE)	**Any grade**	**Grade1**	**Grade2**	**Grade3**	**Grade4**	**Grade5**
Leukopenia	49 (85)	11 (15)	29 (41)	20 (28)	0	0
Neutropenia	50 (70)	17 (24)	18 (25)	14 (19)	1 (1)	0
Anemia	44 (62)	33 (46)	9 (5)	2 (3)	0	0
Thrombocytopenia	33 (46)	29 (41)	2 (3)	2 (3)	0	0
AST elevation	33 (46)	28 (39)	4 (6)	1 (1)	0	0
Fatigue	30 (42)	23 (32)	6 (8)	1 (1)	0	0
Hand-foot syndrome	24 (34)	16 (23)	7 (10)	1 (1)	0	0
Nausea	23 (32)	16 (23)	7 (10)	0	0	0
Cr elevation	17 (24)	14 (20)	3 (4)	0	0	0
ALT elevation	15 (21)	12 (17)	1 (1)	2 (3)	0	0
Stomatitis	11 (15)	11 (15)	0	0	0	0
Vomitting	9 (13)	5 (7)	4 (6)	0	0	0
Alopecia	7 (10)	6 (8)	1 (1)	/	/	/
Diarrhea	6 (8)	4 (6)	2 (3)	0	0	0
BUN elevation	2 (3)	2 (3)	0	0	0	0
Thromboembolic event	1 (1)	/	0	0	0	1 (1)
Maximum grade any AE	69	13 (18)	30 (42)	24 (34)	1 (1)	1 (1)

cases were discontinued due to adverse events such as infection, myelosuppression, and weight loss.

Discussion

Previous studies investigating combined XC therapy in patients with MBC have reported positive primary RR, PFS, and OS results compared with the historical reports describing capecitabine as monotherapy[9, 12, 13]. Our study group previously reported the efficacy and toxicity of XC combination chemotherapy in patients who previously had the anthracycline therapy[11]. In this prospective cohort study, we aimed to reveal how XC therapy was used in clinical practice, and to investigate its efficacy and safety. Thus, this prospective observational study did not specify the timing of administration or disease state, but virtually all of the registered cases were upfront for metastatic breast cancer. For patients without prior chemotherapy for metastatic lesions, response rates were comparable to our previous study.

After completing this study, we found that the XC regimen was preferably used in three specific patient groups, the first of which was older adults. We compared the effects of treatment and the frequency of adverse events in patients aged 65 years or older with those aged 64 years or younger. More than 80% of the patients enrolled in the present cohort study were aged >50 years; in particular, 34% were over 65 years. The clinical benefit rate in these patients was 58%, which was comparable to that of the younger group (Table 2). Same is true for PFS and OS (Fig. 1). It is important to minimize the side effects in older patients with decreased activity of daily living and multiple comorbidities. They may not be able to tolerate strong intravenous anticancer drugs that can possibly induce severe adverse events. In the present study, the incidence of grade ≥ 3 adverse events was 36%, most of which showed controllable leukopenia and neutropenia except for 2 patients who experienced grade3 anemia and elevated liver enzymes (Table 4). One patient died of pulmonary embolism after completing one cycle of treatment. It is thought that advanced cancer was most likely cause of this thromboembolic event. Although hand-foot syndrome is one of the most frequent and troublesome adverse events for capecitabine, but grade ≥3 was recorded in only 1 patient.

The second potential candidate for XC therapy is patients with non-life-threatening bone or lung metastases. We investigated the therapeutic effects according to the site of metastasis based on CBR (Table 3). More than 80% of patients with bone or lung metastases can achieve clinical benefits; even in 65% of patients with liver metastases, an increase in tumor size can be controlled for ≥6 months. Although the XC regimen is unlikely to obtain CR, this study showed XC can control tumor progression to some extent. Moreover, this regimen can also play an important role in postponing the onset of symptoms or in mitigating the severity of symptoms associated with tumor progression.

The third candidate for XC therapy is those who had not receive 5-FU prior to this study. In the current prac-

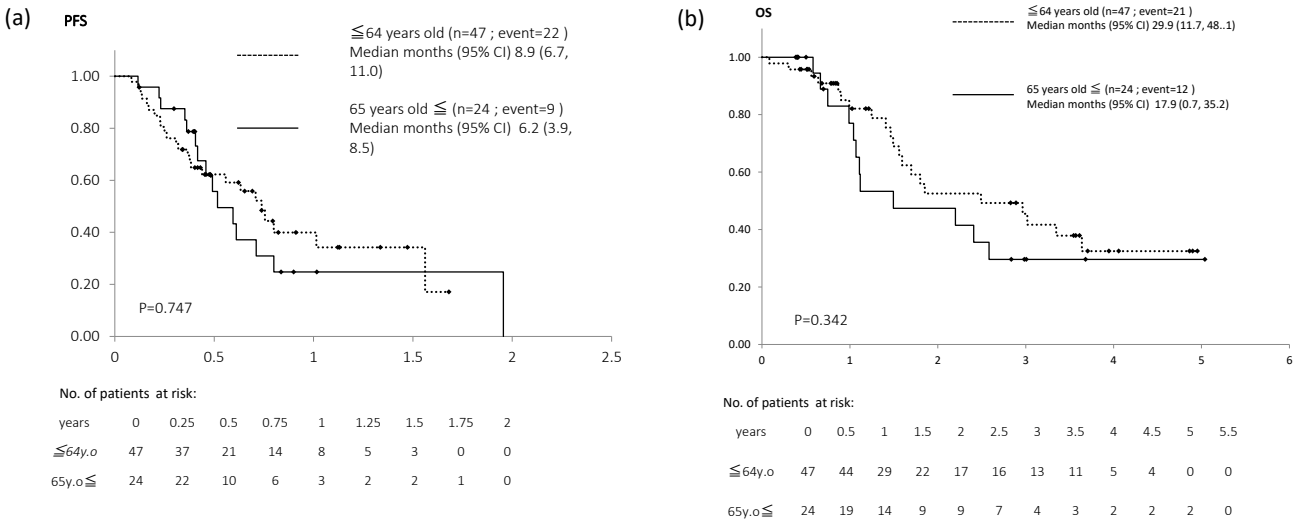

Fig 1. Kaplan-Meier Estimates of Progression-free Survival and Overall Survival by age at the treatment
A solid line is shown for patients over 65, while a dotted line for patients under 65. Dot marks indicate censored patients at the last time when the patient were confirmed to be alive with no event. Panel (a) shows the Kaplan-Meier estimates of progression-free survival and Panel (b) shows that of overall survival.

tice, anthracycline and taxanes are used as a perioperative chemotherapy, but 5-FU or alkylating agents are not often included in an adjuvant therapy. Thus, XC combination appears to be suitable regimen for recurrent disease. Indeed, 62% of the patients had received adjuvant chemotherapy, of which 39% received anthracyclines, 28% received taxanes, and only 13% received 5-FU (Table 1).

In this cohort study, 43 (63%) patients were chemonaïve for metastatic sites, and all patients, except for one, received a second-line treatment. The objective RR, which was the primary endpoint of this study, was 28.1%. The chemo-naïve group had an objective RR of 36%, while the second-line and beyond group had an objective RR of 16% (Table 2). Other studies reported that XC therapy gave rise to the objective RR with no previous chemotherapy was 30%–36%[11-13], and second-line chemotherapy for MBC 13%–35%[14], which were comparable to our result. For chemotherapy-naïve patients, the median PFS and OS in the present study was 8.5 months, and 35.6 months, respectively, while PFS of 11.3 months and OS of 26.7 months for paclitaxel and bevacizumab combination in the E2100 trial[15]. Although PFS might be shorten compared with that of E2100 trial, OS was comparable indicating that the XC combination does not seem to interfere subsequent therapy.

The discrepancy between the OS and PFS results may be explained by the fact that XC is a mild and durable regimen that can be administered for a longer period of time with a gradual effect and tolerable adverse events. Indeed, 60% of the patients were able to continue treatment for longer than 6 months due to good tolerance to XC. It is interesting to notice that there were 7 and 1 patients who reached PR and CR beyond 6 months of treatment, respectively.

This study was planned as a cohort study examining the effects of XC treatment in clinical practice. Therefore, there was not much intervention in case selection and follow-up methods on the protocol. This is considered to be the reasons why the response rate was lower than that of the phase II study we conducted earlier.

In conclusion, XC combination is a useful regimen as a front-line therapy for MBC unless the patient has a life-threatening disease. It has tolerable adverse events which are acceptable to the patients, and long-term treatment is possible.

Support information:
This work was supported by non-profit organization of the Clinical Hematology-Oncology Treatment Study Group (CHOT-SG) for conducting the study.

Ethical approval:
Informed consent was obtained from all individual participants included in this study. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with 1964 Helsinki declaration and its later amendments, Good Clinical Practice guidelines, and other local regulatory requirements. This study complies with the current laws of Japan. The study protocol and its amendments were approved by the institutional review board at each study institute. This study has been registered with the University Hospital Medical Information Network Center (ID: UMIN000044444).

Conflict of interest:
KM, MY, RN, YY, and SM received honoraria from Chugai. All remaining authors have no conflicts of interest to declare.

Acknowledgement:
The authors all thank Ms. Yukimi Itoh, Noriko Ikoma and Etsuko Kumagawa for collecting and cleaning the clinical data and extensive secretarial work. The authors also would like to thank the patients who took part in the trial and their families, as well as the staff who assisted with the study at each site.

Author contributions:

KM, MT, RN, YY, SM, and KT designed, conducted, and coordinated the clinical trial. KM performed the mathematical and statistical analyses. KM, MT, MY, RN, YY, and HU enrolled patients into this trial and collected the majority of the data. KM wrote the manuscript. All authors discussed, read, and approved the manuscript.

Availability of data and material:

Qualified researchers may request access to data by contacting the corresponding author.

References

1) Gradishar WJ, Anderson BO, Abraham J, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18(4):452-78.
2) 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(1):90-8.
3) Miwa M, Ura M, Nishida M, et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5 fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer. 1998;34(8):1274-81.
4) Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer. 2004;40(4):536-42.
5) Lee SH, Lee J, Park J, et al. Capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Med Oncol. 2004;21(3):223-31.
6) Sawada N, Ishikawa T, Fukase Y, et al. Induction of Thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol / taxotere in human cancer xenografts : Clin Cancer Res. 1998;4(4):1013-9.
7) Endo M, Shinbori N, Fukase Y, et al. Induction of thymidine phosphorylase expression and enhancement of efficacy of capecitabine or 5'-deoxy-5-fluorouridine by cyclophosphamide in mammary tumor models. Int J Cancer. 1999;83(1):127-34.
8) O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002 ;20(12):2812-23.
9) Harvey VJ, Sharples KJ, Isaacs RJ, et al. A randomized phase II study comparing capecitabine alone with capecitabine and oral cyclophosphamide in patients with advanced breast cancer-cyclox II. Ann Oncol. 2013;24(7):1828-34.
10) Ohno S, Mitsuyama S, Tamura K, et al. Dosage of capecitabine and cyclophosphamide combination therapy in patients with metastatic breast cancer. Anticancer Res. 2007;27(2):1009-13.
11) Tanaka M, Takamatsu Y, Anan K, et al. Oral combination chemotherapy with capecitabine and cyclophosphamide in patients with metastatic breast cancer: A phase II study. Anticancer Drugs. 2010;21(4):453-8.
12) Wang Z, Lu J, Leaw S, et al. An all-oral combination of metronomic cyclophosphamide plus capecitabine in patients with anthracycline- and taxane-pretreated metastatic breast cancer: A phase II study. Cancer Chemother Pharmacol. 2012;69(2):515-22.
13) Yoshimoto M, Takao S, Hirata M, et al. Metronomic oral combination chemotherapy with capecitabine and cyclophosphamide: A phase II study in patients with HER2-negative metastatic breast cancer. Cancer Chemother Pharmacol. 2012;70(2):331-8.
14) Puglisi F, Rea D, Kroes MA, et al. Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: A systematic review. Cancer Treatment Reviews. 2016;43:36-49.
15) Gray R, Bhattacharya S, Bowden C, et al. Independent review of E2100: A phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. J Clin Oncol. 2009;27(30):4966-72.