Oral combination chemotherapy with capecitabine and cyclophosphamide in patients with metastatic breast cancer: a phase II study

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Capecitabine (Xeloda, X) and cyclophosphamide (C) can be given orally and they have synergistic effects with nonoverlapping toxicities in preclinical studies. A phase I study of the XC combination therapy was conducted in patients with metastatic breast cancer (MBC) and determined the recommended dose and schedule of 1657 mg/m^2/day capecitabine and 65 mg/m^2/day cyclophosphamide given orally for 2 weeks at a 3-week interval. A phase II study of the oral XC regimen was then conducted. This study enrolled patients with HER2-negative MBC who were earlier treated with anthracyclines. XC was given at the recommended doses on a 3-week schedule for at least six courses unless disease progression or unacceptable toxicities occurred. The primary endpoint was the response rate. Progression-free survival, overall survival, and adverse events were investigated as secondary endpoints. Forty-eight patients with the median age of 58 (range 32–72 years) years were registered. Three patients withdrew by choice before starting the treatment. A complete response was obtained in two of the 45 evaluable patients, and partial response in 14, resulting in an overall response rate of 35.6%. The median progression-free survival and overall survival were 199 (115–231) days and 677 (437∼) days, respectively. Grade 3 neutropenia and leukopenia developed in 11%, and that of anemia and thrombocytopenia in 2% patients. Nonhematological toxicities were mild. Hand–foot syndrome was observed in 14 patients but no one had grade 3–4 toxicity. Oral XC combination is effective with acceptable toxicities in patients with MBC. *Anti-Cancer Drugs* 21:453–458 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Anthracycline and taxane-containing regimens are standard for first-line chemotherapy in metastatic breast cancer (MBC). However, the use of these agents has shifted to earlier in the course of disease including the adjuvant setting, and an increasing number of patients has experienced a recurrence after treatment with these agents, leading to the need to develop a new chemotherapy regimen for MBC with no cross-resistance to anthracyclines and taxanes.

Capecitabine (Xeloda; Hoffmann-La Roche Inc., Basel, Switzerland) is an orally active agent that is metabolized to 5-fluorouracil (5-FU) by a three-step enzymatic process and delivered selectively to the neoplastic tissue [1]. After gastrointestinal absorption, capecitabine is hydrolyzed in the liver, deaminated by cytidine deaminase, an enzyme located principally in the hepatic and neoplastic tissue, and then catalyzed by thymidine phosphorylase. As thymidine phosphorylase activity is higher in neoplastic tissue in comparison with normal tissue, 5-FU is preferentially generated in neoplastic tissue. Clinical trials show that capecitabine monotherapy is active in anthracycline and taxane-refractory MBC [2–6]. In xenograft and mammary tumor models, administration of taxanes or cyclophosphamide is shown to upregulate the thymidine phosphorylase levels in neoplastic tissue, and combination therapy of these agents with capecitabine shows synergistic antitumor activity without significant potentiation of toxicity [7,8]. In humans, the efficacy of the combination of capecitabine and docetaxel was clinically shown in a phase III study in which this combination therapy resulted in a significant superior time to progression and overall survival (OS) with a manageable toxicity profile in comparison with docetaxel monotherapy [9].

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The oral administration of antineoplastic agents is more convenient, while also enabling the application of outpatient therapy, which is considered to improve the quality of life in comparison with hospital-based therapy in patients with advanced cancer [10]. Both capecitabine and cyclophosphamide are active agents for breast cancer and can be administered orally. A combination of doxifliridine, an intermediate metabolite of capecitabine and cyclophosphamide is effective treatment for MBC [11,12]. Findlay *et al*. [13] also showed the feasibility of the capecitabine and cyclophosphamide combination. A phase I study of capecitabine and cyclophosphamide (XC) combination therapy was conducted in patients with MBC and determined the recommended dose of both agents [14]. This study is a prospective multicenter phase II study to investigate the efficacy of the XC combination in patients with anthracycline-pretreated MBC.

Patients and methods

Patients and study design

This was a phase II, open-labeled and multicenter study that was conducted by the Kyushu Breast Cancer Study Group. The eligibility criteria for the study included histologically confirmed breast cancer with inoperable or recurrent disease; women aged from 20 to 74 years; Eastern Cooperative Oncology Group performance status of 0–2; a measurable lesion according to the Response Evaluation Criteria in Solid Tumors; HER2 status negative defined as immunohistochemistry staining (score 0 or 1) or negative for fluorescence in-situ hybridization; earlier treatment with anthracycline; no earlier taxanes for the treatment of MBC (taxane-containing neoadjuvant and adjuvant therapies were allowed if taxanes were discontinued for longer than 12 months before this study); a maximum of one earlier chemotherapy regimen for advanced or metastatic disease; adequate hematological parameters, that is, neutrophil counts $\geq 2 \times 10^9$/l, platelet counts $\geq 100 \times 10^9$/l, and hemoglobin ≥ 9 g/dl; creatinine clearance ≥ 50 ml/min; serum total bilirubin ≤ 1.25 times the upper normal limit, and aspartate aminotransferase (AST) and/or alanine aminotransferase ≤ 1.5 times the upper normal limit; and normal electrocardiogram. Exclusion criteria included patients treated earlier with capecitabine or a combination of doxifluridine and cyclophosphamide. The planned sample size was 60 patients with a null hypothesis for overall response rate (ORR) $\leq 25\%$, a one-side $\alpha = 0.05$ and power 80% to detect a clinically meaningful ORR of $\geq 40\%$. A total of 70 patients were required to account for an inevaluable rate of 10%. The study was approved by the institutional review board at each participating center and all patients provided their written informed consent.

Study treatment

The doses of capecitabine and cyclophosphamide were determined according to the earlier phase I trial. A dose of 1657 mg/m^2/day of capecitabine and 65 mg/m^2/day cyclophosphamide was given orally twice daily on days 1–14. The treatment was to be repeated at a 3-week interval for at least 6 cycles until disease progression.

The next cycle of treatment was started if the neutrophil counts were $\geq 1.5 \times 10^9$/l, platelet counts $\geq 75 \times 10^9$/l, and hemoglobin ≥ 8 g/dl; serum creatinine ≤ 1.5 times the upper normal limit; serum total bilirubin ≤ 1.5 times the upper normal limit, and AST and/or alanine aminotransferase were ≤ 2.5 times the upper normal limit. Treatment was interrupted if patients experienced an adverse event classified as grades 2, 3, or 4 as defined by 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 after resolution to grade 0–1. Subsequent occurrences of the same grade 2 toxicity were managed by treatment interruption followed by a 25% dose reduction. If grade 3 or 4 toxicity occurred, 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, treatment was interrupted until the toxicity resolved to grade 0–1 and treatment was then 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.

Study assessments

Tumor lesions were measured using Response Evaluation Criteria in Solid Tumors [15] at baseline, and tumor response was assessed after every two cycles of XC therapy. Hematological and nonhematological toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria version 3.0.

The primary endpoint of this study is to evaluate the ORR produced by oral XC treatment in patients with MBC. The secondary objectives included progression-free survival (PFS), OS, and toxicity. Remission rates were compared using the χ^2 test. PFS and OS estimates were calculated using the Kaplan–Meier method and compared with the log-rank test. Tests for comparisons were regarded as being significant if the two-sided P value was less than 0.05.

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 assignment to this study until death from any cause. Patients who started a new treatment were censored for progression as of the date of the start of new treatment. Surviving patients who were progression free were censored at the last date of contact. All eligible patients who received at least one dose of XC therapy were included in the intent-to-treat analysis of efficacy and in the safety proportion.

Results

Patient population

Forty-eight patients were entered into this study between July 2005 and December 2007. The trial was terminated prematurely because of poor accrual. The planned 80% power of hypothesis testing was not ensured because of shortage of sample size. Nevertheless, the α error was of the ensured planned level and hypothesis testing remained valid. The study group was therefore judged to have yielded sufficient information on the relative efficacy and safety of this regimen. Patient characteristics are shown in Table 1. The median age was 59 years (range 32–72). Performance status was 0 in 40, 1 in seven, and 2 in one patient. There were 33 post-menopausal women. Estrogen receptor (ER) and progesterone receptor (PgR) were positive in 30 and 23 patients, respectively, negative in 14 and 19 patients, respectively, and unknown in four and six patients, respectively. Fourteen patients had metastatic disease in the lung, 20 in liver, 16 in bone, 13 in lymph nodes, four in skin, three in pleura, and 12 at other sites. Nine patients had received chemotherapy as a neoadjuvant chemotherapy, as did 43 for postoperative adjuvant setting before this study was begun, and 31 for the treatment of inoperable or recurrent diseases. All 48 patients had earlier anthracycline-containing chemotherapy. Twenty-two patients had been treated with taxanes as a neoadjuvant or adjuvant chemotherapy, and had subsequently relapsed. The interval between taxane use and relapse was 12–77 (median 31) months. Seventeen patients had received fluoropyrimidine-containing chemotherapy other than capecitabine or a doxifluridine and cyclophosphamide combination. Thirty-five patients had hormonal treatment. Three patients never received the protocol treatment by their own choice after the informed consent was obtained, and therefore, 45 patients were evaluable for efficacy and toxicity.

Table 1 Patient characteristics

Age, years	
Median (range)	58 (32–72)
Performance status, 0/1/2	40/7/1
Diagnosis at registration	
Inoperable disease/recurrent disease	4/44
Histological classification	
Invasive/noninvasive/unknown	45/0/3
Hormone receptor status	
ER+/−/unknown	30/14/4
PgR+/−/unknown	23/19/6
Metastatic sites	
Lung/liver/bone/lymph node/skin/pleura/other	14/20/16/13/4/3/12
Prior treatment	
Neoadjuvant treatment +/−	9/39
Adjuvant treatment +/−	43/5
Treatment for metastatic breast cancer +/−	31/17
Prior antineoplastic agents	
Anthracyclines	48
Taxanes	22
Fluoropyrimidines	17
Cyclophosphamide	43
Endocrine therapy	35

ER, estrogen receptor; PgR, progesteron receptor.

Response and survival

A complete response (CR) was obtained in two (4.4%) of 45 patients, and a partial response (PR) in 14 (31.1%), resulting in ORR of 35.6%. Twelve patients had stable disease (SD) and 13 had progressive disease, whereas four were not evaluable (Table 2). When the treatment responses were analyzed according to hormone receptor (HR) status, ORR was 35.5%, including one CR and four PR in 31 patients with HR positives, whereas it was 41.7% including one CR and four PR in 12 patients with HR negatives.

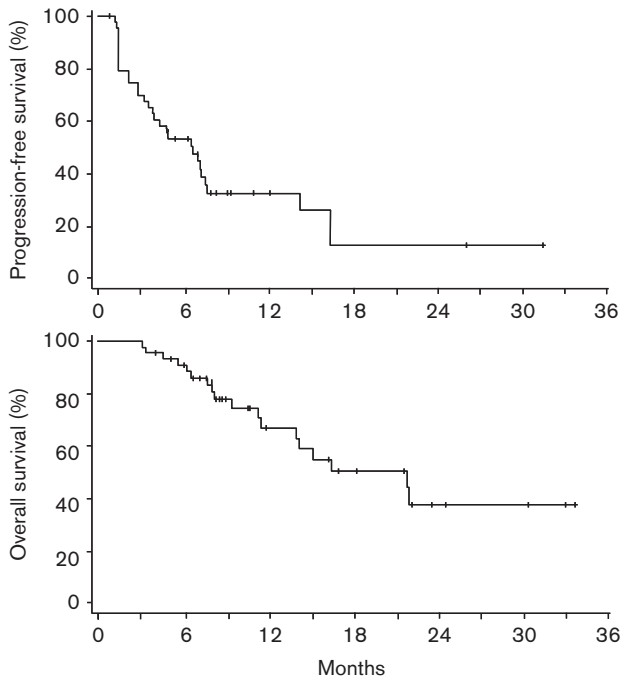
The PFS and OS are shown in Fig. 1. The median PFS was 199 days [95% confidence interval (CI): 115.0–231.0 days], and the median OS was 677 days [95% CI: 437.0–not applicable (NA)]. The median PFS and OS were 147 days (95% CI: 97.0–231.0 days) and 677 days (95% CI: 359.0–NA), respectively in HR-positive patients, and 220.5 days (95% CI: 114.0–NA) and NA, respectively in

Table 2 Response to the treatment

	n	CR	PR	SD	PD	NE	ORR (%)
All patients	45	2	14	12	13	4	35.6
Classified by HR status							
HR +	31	1	10	7	10	3	35.5
HR −	12	1	4	5	2	0	41.7

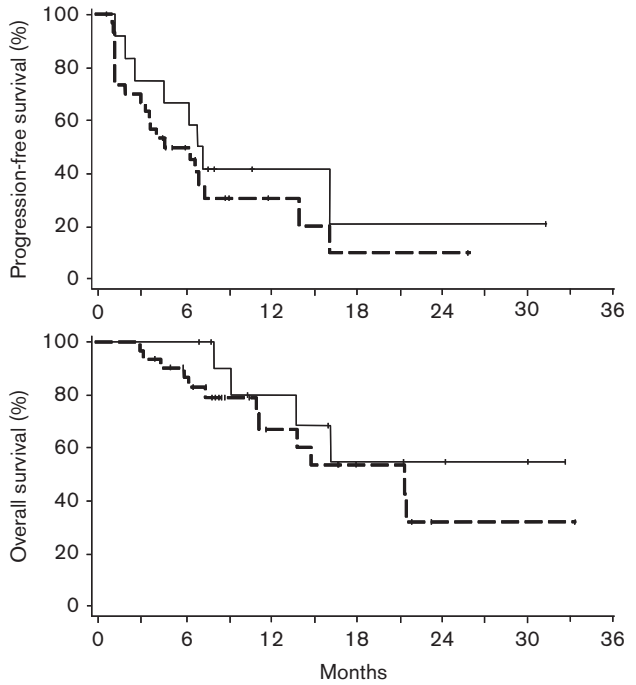
CR, complete response; HR, hormone receptor; *n*, number of patients; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Fig. 1



The progression-free survival time and the overall survival time for 45 patients who received oral XC therapy by Kaplan–Meier method. XC, capecitabine and cyclophosphamide.

Fig. 2



The progression-free survival time and the overall survival time were analyzed separately according to hormone receptor (HR) status by the Kaplan–Meier method. The data of HR-positive patients were shown in the straight line and those of HR-negative in the dotted line.

HR-negative patients (Fig. 2). No significant difference was observed in either PFS or OS between HR-positive and negative groups ($P = 0.43$ and $P = 0.60$, respectively). There was a trend for patients who achieved CR and PR to have a longer OS than those with SD and progressive disease, but the difference was not statistically significant (data not shown, median OS; not reached vs. 472 days, $P = 0.07$).

Toxicity

The hematological and nonhematological toxicities are shown in Table 3. Grade 3 leukopenia was observed in five (11%), neutropenia in five (11%), thrombocytopenia in one (2%), and anemia in one (2%) of 45 patients. Nonhematological toxicities were very mild. The serum alkaline phosphatase and AST levels were elevated to a grade 3 level in two (4%) and one (2%) patients. One of these patients had hepatitis C virus-positive chronic hepatitis, and another had metastatic liver disease. Grade 3 anorexia developed in two (4%), and diarrhea, nausea, and vomiting in one (2%) patients. Hand–foot syndrome (HFS) was observed in 14 (31%), but no one developed grade 3–4 HFS.

The following cycle of XC was delayed in 17 (38%) by less than 7 days owing to neutropenia in seven, diarrhea in three, fatigue in three, vomiting in two, and others in two patients. The treatment dose was reduced in six (13%), caused by neutropenia in four, nausea in one and vomiting in one patient. Three patients (7%) decided to discontinue the treatment because of nausea, vomiting and diarrhea and HFS, but none were greater than grade 2. Two patients were hospitalized for the treatment of local pain in addition to nausea, vomiting, and diarrhea.

Table 3 Hematological and nonhematological toxicities

	Grade 1	Grade 2	Grade 3	Grade 4	≥ Grade 3 (%)
Leukopenia	3	6	5	0	11
Neutropenia	6	20	5	0	11
Anemia	10	5	1	0	2
Thrombocytopenia	6	0	1	0	2
Diarrhea	0	3	1	0	2
Nausea	9	6	1	0	2
Vomiting	5	0	1	0	2
Anorexia	12	5	2	0	4
Stomatitis	4	0	0	0	0
Fatigue	11	5	0	0	0
Hand–foot syndrome	12	2	0	0	0
Hyperpigmentation	9	0	0	0	0
Alopecia	3	1	–	–	–
Pain	0	3	0	0	0
Hypoalbuminemia	4	2	0	0	0
Hyperbilirubinemia	7	1	0	0	0
Elevated AST	14	5	1	0	2
Elevated ALT	15	3	0	0	0
Elevated ALP	14	1	2	0	4
Elevated Cr	2	1	0	0	0

ALT, alanine aminotransferase; ALP, alkalinephosphatase; AST, aspartate aminotransferase; Cr; creatinine.

Discussion

The efficacy of capecitabine has been investigated in patients with MBC who were treated earlier with anthracyclines. The ORRs usually range from 15 to 35%, and the median time to progression (TTP) and OS range from 3.0 to 4.9 months and 10.1 to 16.0 months, respectively [2–6]. Taxanes are the treatment of choice generally for these patients. Docetaxel and paclitaxel induce ORRs of 23–42% and 17–29% with the median TTP of 4.0–6.3 and 3.0–4.2 months, and the median OS of 9.8–15.4 and 10.5–12.7 months, respectively [16–20]. A randomized phase II study comparing capecitabine with paclitaxel showed that no significant difference was observed in the ORR (36 vs. 26%), the median TTP (3.0 vs. 3.1 months) and the median OS (7.6 vs. 9.4 months) between capecitabine- and paclitaxel-treated patients [21]. Paclitaxel was associated with more alopecia, peripheral neuropathy, myalgia, and neutropenia, whereas capecitabine with diarrhea, vomiting, and HFS. As a result, the efficacy of capecitabine is therefore indicated to be comparable with taxanes, whereas its toxicity profiles are more favorable.

The cytotoxic effects of capecitabine depend on the activity of thymidine phosphorylase located in tumor cells because capecitabine is finally converted to 5-FU by this enzyme [1]. Cyclophosphamide is shown to upregulate thymidine phosphorylase levels in tumor cells and

theoretically increase the cytotoxic effects of capecitabine [8]. A combination of doxifluridine, an intermediate metabolite of capecitabine, and cyclophosphamide is more effective than doxifluridine alone as a postoperative adjuvant chemotherapy [12]. This study therefore evaluated the XC combination therapy for the patients with MBC, and found that the ORR was 35.6% and the median PFS and OS were 199 days (6.5 months) and 677 days (22.3 months), respectively. Clinical studies of capecitabine monotherapy show that ORR, the median TTP and OS are 15–35%, 3.0–4.9 and 10.1–16.0 months, respectively [2–6]. Although this was not a randomized study between XC and capecitabine alone, XC was not worse or even better in survival in comparison with capecitabine monotherapy.

Capecitabine has been combined with taxanes, either paclitaxel or docetaxel by the same concept as XC, that is, the enhancement of thymidine phosphorylase by taxanes. The dose and schedule of capecitabine have run from 1650 to 2000 mg/m^2/day for 14 days in a 3-week cycle [22–24]. ORR is reported to be 51–55%. TTP and OS are 8.1–10.6 and 16.5–29.9 months, respectively. However, 11–18% of the patients experience grade 3–4 HFS. The patients in this study never experienced grade 3–4 HFS and even if HFS developed, the degree was so mild that the patients were able to continue for months and a few patients received the regimen longer than 2 years because of persistent SD on the XC regimen.

Loss of hair is another important adverse event for female patients, especially in young females who are actively working. XC was associated with alopecia in less than 10% of the patients and was grade 1 in three and grade 2 in one patient. Taxanes have grade 2–3 alopecia in virtually all patients [20]. As advanced or recurrent breast cancer is considered to be incurable, XC therefore appears to be more useful than a taxane–capecitabine combination.

ORR and PFS in XC may be comparable or somewhat lower and shorter than that of taxane–capecitabine, but the OS of XC is close to 2 years, which is comparable with that of taxane combination, which ranges from 16.5 to 29.9 months [22–24]. It is tempting to speculate that longer administration of XC is permitted to control the disease longer because of good patients' compliance and little toxicity in XC.

Earlier clinical studies showed that the pathological CR rate in HER2 –/ER + patients (luminal A) in the neoadjuvant setting was remarkably low in comparison with that in other subtypes when docetaxel was given after FEC (5-FU, epirubicin, cyclophosphamide) [25]. Patients with HER2 –/ER + breast cancer experience few benefits from the administration of paclitaxel as adjuvant chemotherapy after doxorubicin and cyclophosphamide [26]. Although the effects of taxanes according to the subtypes have not been analyzed in patients with MBC, the efficacy of taxanes cannot be expected to be as high in HER2 –/ER + patients. This study showed that ORR, the median PFS and OS were 35.5%, 147, and 677 days, respectively, in the HER –/ER + patients treated with the XC regimen, thus indicating that this regimen can be considered to be a good candidate for this subtype.

This study included 12 patients whose breast cancer was negative for ER, PgR, and HER (basal-like). This type of breast cancer is so-called 'triple negative', and generally aggressive in nature [27]. A taxane combination with capecitabine has not been studied so far with regard to this subgroup, and there have been phase I and phase II studies to target triple negative breast cancer which include platinum compounds, taxanes, epidermal growth factor receptor inhibitors, c-kit inhibitors, and anti-vascular endothelial growth factor antibodies [27–29]. Although the number of patients in this study is small, ORR, median PFS and OS were 41.7%, 220.5 days and not reached, respectively, in the 12 patients with triple negatives, and they were no worse than those of the HR positive group. Further study is therefore needed to confirm these results.

In conclusion, the XC combination regimen is therefore considered to be effective with acceptable toxicities in patients with MBC who were treated earlier with anthracyclines. As both capecitabine and cyclophosphamide are orally administered agents, this combination is also convenient for patients who are to be treated on an outpatient basis.

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