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A Randomized Phase II Trial of Capecitabine Plus Vinorelbine Followed by Docetaxel Versus Adriamycin Plus Cyclophosphamide Followed by Docetaxel as Neoadjuvant Chemotherapy for Breast Cancer

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Purpose

Given the promising activity of capecitabine and vinorelbine in metastatic breast cancer, this randomized phase II trial evaluated the efficacy and safety of this combination as neoadjuvant chemotherapy in breast cancer.

Materials and Methods

Patients with operable breast cancer (n=75) were randomly assigned to receive either four cycles of adriamycin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 3 weeks followed by four cycles of docetaxel 75 mg/m^2 every 3 weeks (AC-D) or four cycles of capecitabine 2,000 mg/m^2 (day 1-14) plus vinorelbine 25 mg/m^2 (days 1 and 8) every 3 weeks followed by four cycles of docetaxel 75 mg/m^2 (CV-D). The primary endpoint was pathologic complete response (pCR) in the primary breast (ypT0/is).

Results

Most patients (84%) had locally advanced (n=41) or inflammatory breast cancer (n=22). pCR rates in the primary breast were 15% (95% confidence interval [CI], 7% to 30%) and 11% (95% CI, 4% to 26%) in the AC-D and CV-D groups, respectively. The overall response rates and 5-year progression-free survival rates in the AC-D and CV-D groups were 62% and 64%, and 51.3% (95% CI, 34.6% to 68.0%) and 30.2% (95% CI, 13.3% to 47.1%), respectively. Although both regimens were well tolerated, CV-D showed less frequent grade 3-4 neutropenia and vomiting than AC-D, whereas manageable diarrhea and hand-foot syndrome were more common in the CV-D group.

Conclusion

CV-D is a feasible and active non-anthracycline–based neoadjuvant chemotherapy regimen for breast cancer.

Key words
Breast neoplasm, Neoadjuvant therapy, Anthracyclines, Capecitabine, Vinorelbine

Introduction

Neoadjuvant chemotherapy has become the standard treatment for patients with locally advanced or inflammatory breast cancer [1,2] and has recently been accepted for treatment of patients with operable early breast cancer [3,4]. Although no clear survival benefit over adjuvant chemotherapy has been demonstrated [3,4], neoadjuvant chemotherapy has been favored for improving operability and increasing the probability of breast conservation by reducing the size of the primary tumor and lymph node metastases.

Anthracycline is a key agent involved in neoadjuvant chemotherapy for breast cancer patients, and its concurrent

or sequential combination with taxane has been widely investigated [4-7]. Despite the proven efficacy of anthracycline, rare but lethal long-term cardiac toxicity has been a major concern, particularly for patients with potentially operable and curable disease [6,8,9]. Therefore, non-anthracycline–based regimens have been investigated in the neoadjuvant and adjuvant setting [10-12].

The use of capecitabine and vinorelbine (CV) for treatment of patients with metastatic or recurrent breast cancer have been investigated as a first-line or salvage therapy after failure of anthracycline and taxanes, and both agents were active as monotherapies [13,14]. Based on non-overlapping safety profiles and potential synergistic anti-cancer activity in a preclinical model [15], combined regimens of CV have been evaluated and found to have promising efficacy in chemotherapy-naïve and anthracycline (and/or taxane)–pretreated patients with metastatic breast cancer [13,16,17]. In a previous phase II study conducted in our institution, CV regimen was highly active in anthracycline and taxane–pretreated patients with metastatic breast cancer with an overall response rate of 50% and manageable toxicities [16].

Therefore, we conducted a randomized phase II study to investigate the efficacy and safety of two sequential neoadjuvant chemotherapy regimens, anthracycline and cyclophosphamide (AC) followed by docetaxel (AC-D), and CV followed by docetaxel (CV-D), in patients with locally advanced, inflammatory, and operable early breast cancer. Here, we report the results of our study.

Materials and Methods

This was a non-comparative, open-label, randomized phase II study conducted in a single tertiary institution. The research was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea, and conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All participants provided written informed consent before enrollment.

1. Study population

To be included in this study, patients with localized breast cancer were required to have histologically or cytologically confirmed axillary lymph node metastasis, as well as to have had no previous treatment for breast cancer, including surgery, hormonal therapy, or chemotherapy. Patients with locally advanced breast cancer, defined as a tumor diameter > 5 cm by ultrasonography or magnetic resonance imaging (MRI), or inflammatory breast cancer were also eligible for this study. Further eligibility criteria included an age between 18 and 70 years, an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2 and adequate hematologic (absolute neutrophil count [ANC] ≥ 1,500/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin ≥ 10 g/dL), renal (serum creatinine ≤ 1.5 mg/dL), and hepatic function (total bilirubin ≤ 1.5 mg/dL, transaminases and alkaline phosphatase ≤ 2.5 × upper normal limit). Patients were excluded if they had a second primary malignancy (except carcinoma *in situ* in the cervix or adequately treated non-melanoma skin cancer), any distant metastasis, or any serious concomitant systemic disorder.

Pretreatment evaluation included a medical history and physical examination, complete blood counts with differential counts and renal and liver function tests, and echocardiography. Baseline radiological tumor evaluations including bilateral mammography, ultrasonography and MRI, and 18F-fluorodeoxyglucose–positron emission tomography were performed within 4 weeks before enrollment.

2. Treatment

Eligible patients were randomly assigned in a 1:1 ratio to receive either four cycles of adriamycin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 (day 1) every 3 weeks followed by four cycles of docetaxel 75 mg/m^2 every 3 weeks (AC-D), or four cycles of capecitabine 2,000 mg/m^2 (day 1-14) plus vinorelbine 25 mg/m^2 (days 1 and 8) every 3 weeks followed by four cycles of docetaxel 75 mg/m^2 (CV-D). Randomization was stratified by age (≤ 35 years vs. > 35 years) and cancer type (inflammatory vs. non-inflammatory breast cancer). Capecitabine was administered orally twice a day. As prophylaxis for potential docetaxel hypersensitivity reactions, intravenous dexamethasone 10 mg, phenyramine maleate 45.5 mg, and ranitidine 50 mg or cimetidine 300 mg were administered before each cycle of docetaxel, and 4 mg of oral dexamethaonse was administered twice daily on day 2-4. Prophylactic use of colony-stimulating factors was not permitted.

Doses of study drugs were interrupted or modified for grade 3-4 hematological toxicities and grade 2-4 non-hematological toxicities according to the protocol. For hematologic toxicities, dose resumption could be delayed for a maximum of 2 weeks and given only with an ANC of ≥ 1,500/mm^3 and platelet counts of ≥ 100,000/mm^3. In patients who experienced febrile neutropenia, the doses of all study drugs except capecitabine were reduced by 25% in all subsequent cycles. For all grade 3 or higher non-hematologic toxicities, treatment was delayed until the patient recovered to grade 1 or less.

Following completion of eight cycles of chemotherapy, patients underwent surgery within 4 weeks of the last dose

of chemotherapy, and the type of surgery was determined by the attending surgeons. Complete axillary lymph node dissection and pathological review were performed for all patients, including those who underwent breast-conserving surgery. In patients who showed no response or progression in the first four-cycle phase of AC or CV, surgery was performed with or without additional administration of docetaxel according to the physician's discretion. After surgical resection, adjuvant radiotherapy was administered within 4 weeks of surgery for patients with axillary lymph node-positive locally advanced or inflammatory breast cancer and those who underwent breast-conserving surgery. Adjuvant endocrine therapy commenced 1 month after the completion of chemotherapy for patients with hormonal receptor–positive breast cancer, and the details of treatments for individual patients were determined by attending physicians based on the National Comprehensive Cancer Network and St. Gallen clinical guidelines.

3. Efficacy and safety assessments

Response assessments were performed by palpation and imaging modalities, which were used at baseline and after the first phase of treatment (four cycles of AC or CV) and the complete course of chemotherapy. Additional imaging was performed if disease progression was clinically indicated. Tumor responses were determined in accordance with Response Evaluation Criteria In Solid Tumors (RECIST) ver. 1.0 [18]. Toxicity assessment, physical examinations, and laboratory tests were performed at each treatment cycle. Until completion of the first cycle of the study treatment, complete blood counts were monitored every week. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 3.0. All surgical specimens from breast and lymph nodes were evaluated for pathological response.

4. Statistics

The primary end point of this study was pathologic complete response (pCR) in the primary breast (ypT0/is), which was defined as complete absence of viable invasive tumor cells on postoperative pathologic examination, regardless of residual carcinoma *in situ*. Other previously suggested definitions of pCR, including no invasive residual carcinoma in lymph nodes (ypN0) and no invasive residual carcinoma in the breast and lymph nodes (ypT0/is, ypN0), were also assessed. The secondary endpoints were the radiological response rate, progression-free survival (PFS), overall survival (OS), and safety profile. PFS was defined as the time from the date of study enrollment to the first date of progressive disease or death from any cause, and OS was defined as the time from the date of study enrollment to the date of death from any cause.

The Simon two-stage design was applied separately for each study arm and used to detect differences in pCR rates of between 5% (H_0) and 20% (H_1) with a two-sided alpha of 0.1 and power of 90% [19]. Assuming a drop-out rate of 10%, a total of 40 patients were required for each arm. If pCR was not achieved in the first 12 patients in each arm, further patient accrual was not permitted in that arm.

No statistical comparisons were made between treatment arms. Chi-square or Fisher exact tests were used to analyze the categorical variables. The probability of survival was estimated by the Kaplan-Meier method. All analyses were based on the intention-to-treat population. A two-sided p-value of < 0.05 was considered statistically significant, and all statistical analyses were performed using SPSS ver. 18.0 (SPSS Inc., Chicago, IL).

Results

1. Patients

From July 2005 to February 2010, 80 patients were eligible for this study and 75 were randomly assigned to the AC-D (n=39) and CV-D (n=36) arms (Fig. 1). Five eligible patients discontinued the study before randomization due to protocol violation (n=2) and patient decision (n=3). Locally advanced breast cancer (n=41, 55%) was the most common disease type, followed by inflammatory breast cancer (22, 29%) and early breast cancer (12, 16%). All patients had an ECOG performance status of 0 or 1. Hormone receptor and human epidermal growth factor receptor 2 (HER2) were positive in 55% (AC-D vs. CV-D; 59% vs. 50%) and 32% (31% vs. 33%) of patients, respectively. As shown in Table 1, the baseline characteristics were well balanced between the two arms.

Pathologic response was assessable in 70 patients (93%) who underwent surgery after chemotherapy (36 in the AC-D arm and 34 in the CV-D arm). Three patients in the AC-D arm (two for distant metastasis and one for inoperable local progression) and two in the CV-D arm (one each for distant metastasis and patient refusal) did not receive surgery in the AC-D arm. Nine patients (four in the AC-D arm and five in the CV-D arm) underwent surgical resection before completion of the planned study treatment. In the AC-D arm, two of three patients who refused second phase docetaxel after four cycles of AC received four postoperative cycles of docetaxel, while one patient who discontinued second phase docetaxel due to toxicities was not treated with postoperative chemotherapy. In the CV-D arm, three and one

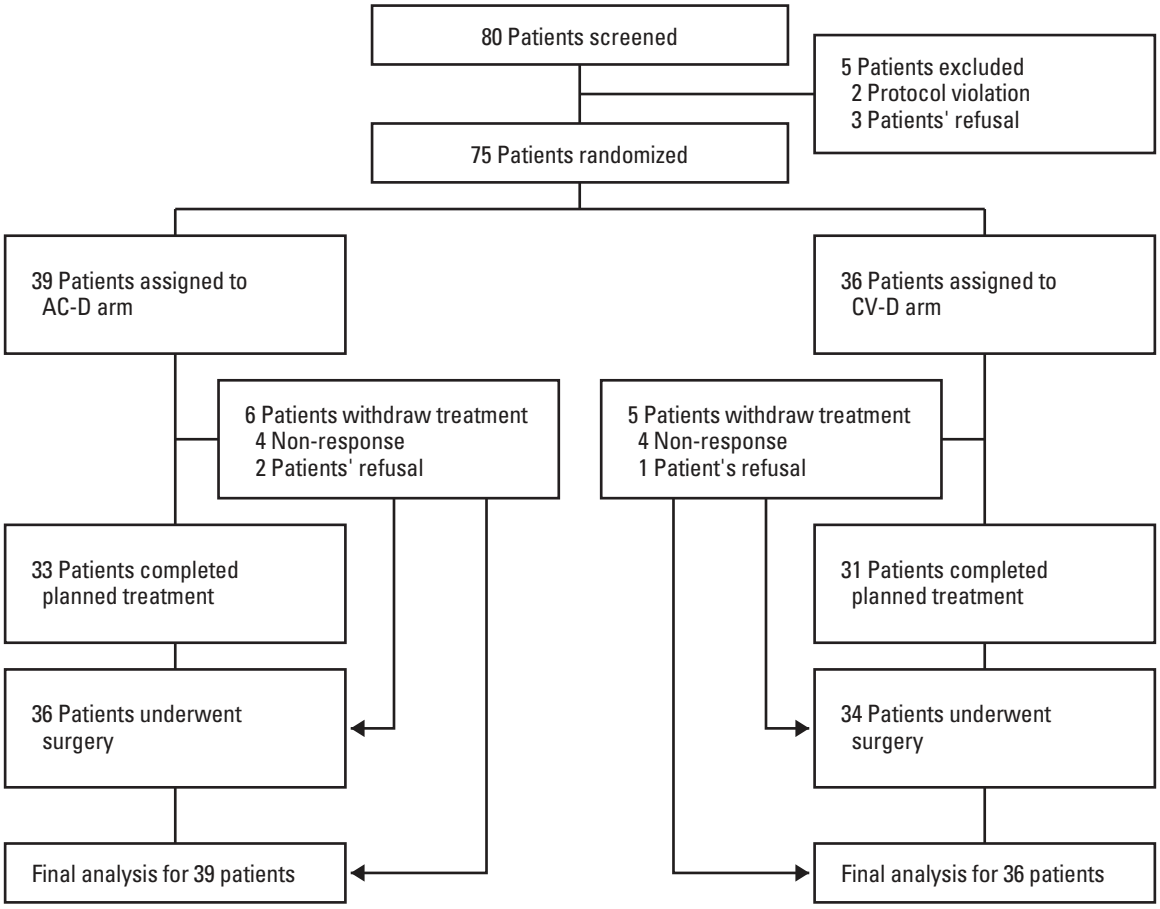

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. AC-D, anthracycline and cyclophosphamide followed by docetaxel; CV-D, capecitabine and vinorelbine followed by docetaxel.

patients received four postoperative cycles of AC and docetaxel, respectively. One patient each in the AC-D and CV-D arms refused postoperative chemotherapy.

Adjuvant radiotherapy and endocrine therapy were administered in all patients who met the prespecified eligibility. During the active recruitment for this study, national health insurance coverage in Korea included adjuvant treatment with trastuzumab. Since then, trastuzumab has been postoperatively administered for patients with HER2-positive breast cancer. Four patients (33% of HER2-positive cases) each in the AC-D arm and the CV-D arm received adjuvant trastuzumab in this study.

2. Efficacy

The rate of pCR in the primary breast (ypT0/is), the primary endpoint of this study, was 15% (n=6; 95% confidence interval [CI], 7% to 30%) in the AC-D arm and 11% (n=4; 95% CI, 4% to 26%) in the CV-D arm. In the AC-D and CV-D arms, no residual tumor in the primary breast (ypT0) was detected in four patients (10%) and three patients (8%), respectively, while no residual tumor was detected in the lymph nodes (ypN0) in 15 patients (38%) and 16 patients (44%), respectively, and no invasive residual tumor in the primary breast and lymph nodes (ypT0/is and ypN0) was detected in five patients (13%) and two patients (6%), respectively (Table 2). In both arms, pCR rates were highest in patients with HER2-positive breast cancer (Table 3). Although a small number of patients per subgroup should be considered, none of the patients assigned to the CV-D arm with hormone receptor–positive, HER2-negative, and triple-negative breast cancer achieved pCR. The pCR rate according to disease type is summarized in Table 4. In both groups, pCR rates were highest in patients with early breast cancer (40% in the AC-D group vs. 29% in the CV-D group).

In this study, radiological response was assessed by MRI and/or ultrasonography (Table 2). In the first phase of treatment (AC or CV), an objective response (complete

Table 1. Patient and tumor characteristics at baseline

Variable	AC-D (n=39)	CV-D (n=36)
Median age (range, yr)	46 (27-70)	42 (24-62)
Median tumor size by MRI (range, cm)	5.5 (2.3-14.0)	5.8 (1-13.0)
Histological grade		
Grade 2	21 (54)	15 (42)
Grade 3	12 (31)	18 (50)
Not available	6 (15)	3 (8)
Type of disease		
Locally advanced breast cancer	21 (54)	20 (56)
Inflammatory breast cancer	13 (33)	9 (25)
Early breast cancer	5 (13)	7 (19)
Hormonal receptor status		
ER+ and/or PR+	23 (59)	18 (50)
ER– and PR–	16 (41)	18 (50)
HER2 status		
Positive	12 (31)	12 (33)
Negative	24 (61)	23 (64)
Not available	3 (8)	1 (3)

Values are presented as number (range or %). AC-D, anthracycline and cyclophosphamide followed by docetaxel; CV-D, capecitabine and vinorelbine followed by docetaxel; MRI, magnetic resonance imaging; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 2. Summary of main efficacy parameters

Variable	Value	
Pathologic response	AC-D (n=39)	CV-D (n=36)
ypT0/is	6 (15)	4 (11)
ypN0	15 (39)	16 (44)
ypT0/is and ypN0	5 (13)	2 (6)
Radiologic response after the first 4 cycles	AC (n=39)	CV (n=36)
Complete response	3 (8)	3 (8)
Partial response	22 (56)	20 (56)
Stable disease	13 (33)	12 (33)
Progressive disease	1 (3)	1 (3)
Overall radiologic response	AC-D (n=39)	CV-D (n=36)
Complete response	5 (13)	5 (14)
Partial response	19 (49)	18 (50)
Stable disease	11 (28)	11 (31)
Progressive disease	4 (10)	2 (6)
Surgical outcome	AC-D (n=36)	CV-D (n=34)
Breast-conserving operation	8 (22)	8 (23)
Modified radical mastectomy	25 (70)	24 (71)
Skin-sparing mastectomy	3 (8)	2 (6)

Values are presented as number (%). AC-D, anthracycline and cyclophosphamide followed by docetaxel; CV-D, capecitabine and vinorelbine followed by docetaxel.

Table 3. Pathologic complete response (pCR, ypT0/is) by hormone receptor and HER2 status

Hormone receptor and HER2 status	AC-D	CV-D	Total
ER+ and/or PR+	3 (3/22, 14%)	0 (0/16)	3 (3%)
ER– and PR–	3 (3/14, 21%)	4 (4/17, 24%)	7 (23%)
HER2+	3 (3/10, 30%)	4 (4/12, 33%)	7 (32%)
HER2–	2 (2/23, 9%)	0 (0/21)	2 (5%)
TNBC	1 (1/7, 14%)	0 (0/7)	1 (7%)

HER2, human epidermal growth factor receptor 2; AC-D, anthracycline and cyclophosphamide followed by docetaxel; CV-D, capecitabine and vinorelbine followed by docetaxel; ER, estrogen receptor; PR, progesterone receptor; TNBC, triple-negative breast cancer.

Table 4. Pathologic complete response (pCR, ypT0/is) by type of disease

Hormone receptor and HER2 status	AC-D	CV-D	Total
Locally advanced breast cancer	1 (1/21, 5%)	2 (2/20, 10%)	3 (7%)
Inflammatory breast cancer	2 (2/12, 17%)	0 (0/9)	2 (10%)
Early operable breast cancer	2 (2/5, 40%)	2 (2/7, 29%)	4 (33%)

pCR, pathologic complete response; HER2, human epidermal growth factor receptor 2; AC-D, anthracycline and cyclophosphamide followed by docetaxel; CV-D, capecitabine and vinorelbine followed by docetaxel.

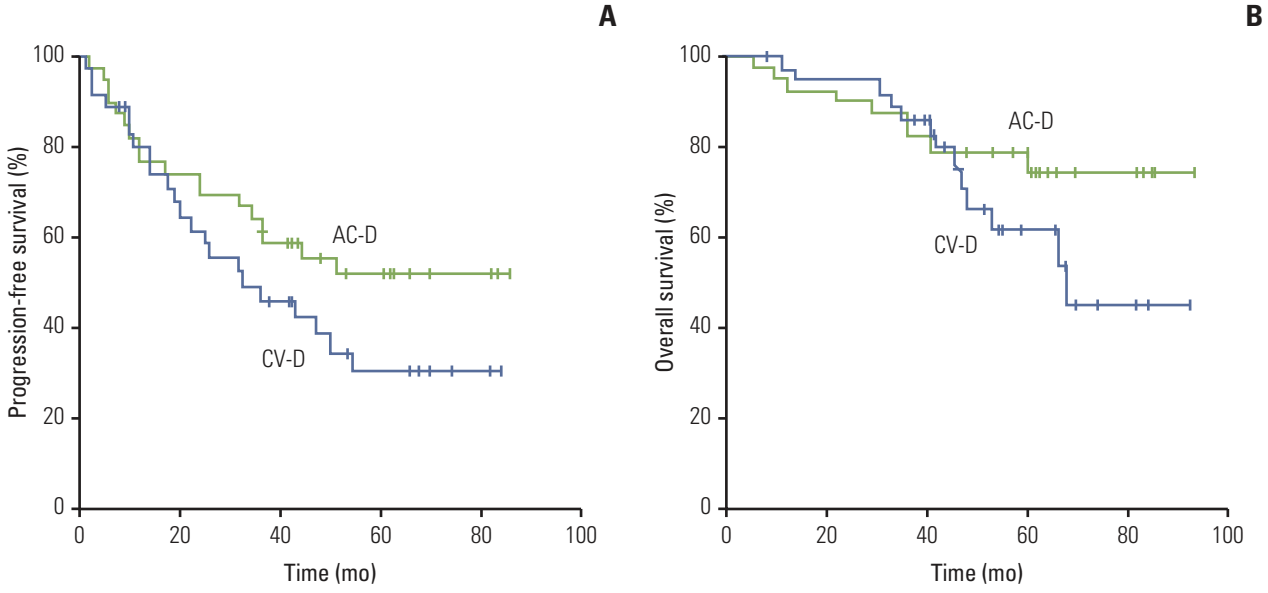

Fig. 2. Progression-free survival (A) and overall survival (B). AC-D, anthracycline and cyclophosphamide followed by docetaxel; CV-D, capecitabine and vinorelbine followed by docetaxel.

Table 5. Adverse events

Toxicity	Grade	AC-D (n=39)		CV-D (n=36)	
		AC (n=39)	D (n=35)	CV (n=36)	D (n=31)
Anemia	All	35 (90)	33 (94)	35 (97)	28 (90)
	G3-4	1 (3)	0	0	0
Neutropenia	All	39 (100)	35 (100)	36 (100)	31 (100)
	G3-4	31 (80)	14 (40)	17 (47)	23 (74)
Thrombocytopenia	All	32 (82)	2 (6)	34 (94)	3 (10)
	G3-4	0	0	0	0
Nausea	All	36 (92)	15 (43)	23 (64)	10 (32)
	G3-4	0	0	0	0
Vomiting	All	24 (62)	4 (11)	10 (28)	1 (3)
	G3-4	4 (10)	1 (3)	0	0
Diarrhea	All	5 (13)	6 (17)	12 (33)	9 (29)
	G3-4	0	0	0	0
Stomatitis	All	20 (51)	12 (34)	13 (36)	14 (45)
	G3-4	0	0	0	0
Neurotoxicity	All	19 (49)	22 (63)	16 (44)	21 (68)
	G3-4	0	0	0	0
Fatigue	All	17 (44)	12 (34)	20 (56)	14 (45)
	G3-4	0	0	0	0
Hand-foot syndrome	All	1 (3)	15 (43)	6 (17)	12 (39)
	G3-4	0	0	1 (3)	3 (10)
Myalgia	All	14 (36)	26 (74)	18 (50)	20 (65)
	G3-4	0	4 (11)	0	0
Edema	All	0	14 (40)	0	11 (36)
	G3-4	0	0	0	0

Values are presented as number (%). AC, anthracycline and cyclophosphamide; D, docetaxel; CV, capecitabine and vinorelbine.

response+partial response) was achieved in 25 (64%) and 23 (64%) patients in the AC-D and CV-D arms, respectively. After the complete course of study treatment, response rates were 62% (n=24) in the AC-D arm and 64% (n=23) in the CV-D arm. Three patients (two in the AC-D arm and one in the CV-D arm) who achieved partial response in the first phase of treatment developed distant metastasis during the second phase of treatment with docetaxel.

With a median follow-up of 53.7 months (range, 8.3 to 93.8 months) in living patients, the median PFS and OS were 33.0 months (95% CI, 10.6 to 55.3 months) and 68.3 months (95% CI, 47.0 to 89.6 months), respectively, in the CV-D arm, whereas those were not attained in the AC-D arm (Fig. 2). The 5-year PFS rate was 51.3% (95% CI, 34.6% to 68.0%) in the AC-D arm and 30.2% (95% CI, 13.3% to 47.1%) in the CV-D arm. The 5-year OS rate was 79.4% (95% CI, 66.7% to 92.1%) in the AC-D arm and 61.3% (95% CI, 42.5% to 80.1%) in the CV-D arm.

3. Safety

The first phase of treatment (four cycles of AC or CV) was completed in 38 of 39 patients assigned to the AC-D arm and all patients in the CV-D arm. The planned second phase of treatment (four cycles of docetaxel) was given in 33 patients (85%) of the AC-D arm and 31 patients (86%) of the CV-D arm. Six patients in the AC-D arm and five in the CV-D arm discontinued study treatment for the following reasons: lack of response (four in each group) and patient decision (two and one, respectively). A total of 292 of 312 planned chemotherapy cycles (94%) were administered to 39 patients assigned to AC-D, and 268 of 288 planned cycles (93%) were given to the 36 patients assigned to CV-D. Doses of all study drugs were reduced and delayed in 13 patients (33%) and 12 patients (31%), respectively, in the AC-D arm and in 13 patients (36%) and 21 patients (58%), respectively, in the CV-D arm. The mean relative dose intensity of docetaxel was maintained at a minimum of 93% in both arms (Fig. 3).

Adverse events were assessed in all randomized patients

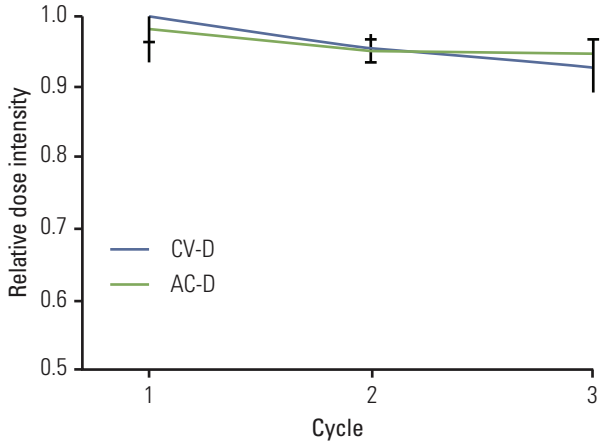

Fig. 3. Relative dose intensity of docetaxel. AC-D, anthracycline and cyclophosphamide followed by docetaxel; CV-D, capecitabine and vinorelbine followed by docetaxel.

and there were no treatment-related deaths. Both treatments were well tolerated and most toxicity was manageable with dose modification or interruption. The adverse events of both arms are summarized in Table 5. Grade 3-4 neutropenia was the most frequent severe adverse event in both groups, being experienced by 31 patients (80%) during the AC phase and 14 (40%) during the subsequent docetaxel phase in the AC-D arm and by 17 patients (47%) during the CV phase and 23 (74%) during the subsequent docetaxel phase in the CV-D arm. Grade 3-4 vomiting was the second most common severe toxicity in the AC-D arm, whereas no patient in the CV-D arm experienced. Seven patients (18%) in the AC-D arm and six (17%) in the CV-D arm experienced febrile neutropenia. No patients had grade 4 non-hematologic toxicities.

Discussion

Although AC-D has been a standard neoadjuvant chemotherapy regimen for node-positive breast cancer, our study showed that CV-D can be a feasible and active non-anthracycline–based regimen for neoadjuvant chemotherapy of breast cancer. pCR in the primary breast, the primary endpoint of this trial, was achieved in 11% of patients assigned to receive CV-D, while it was achieved in 15% of those who received AC-D, and the toxicity profiles between the two regimens differed. The proportion of patients who underwent a breast-conserving operation was also similar between the two arms (CV-D vs. AC-D, 21% vs. 22%). Upon radiological assessment, both regimens showed similar response rates of 64% in the CV-D arm and 62% in the AC-D arm. Nausea and vomiting occurred less frequently in patients who received CV-D than in those with AC-D, whereas manageable diarrhea and hand-foot syndrome were more common in the CV-D arm.

Our findings for the efficacy of CV are in line with results of previous studies. Although most studies were performed in small numbers of patients, the response rates of CV for metastatic breast cancer were 43%-77% in chemotherapy-naïve patients and 33%-50% in pretreated patients [13,16,17]. Furthermore, in a large phase III trial (GeparTrio), the CV regimen was used as a component of response-guided neoadjuvant chemotherapy for early non-responders after two cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) [20]. In that study, an objective response was achieved in 51% of patients who received CV, indicating non-inferiority of CV to TAC in non-early responders to TAC. These data, as well as ours, suggest that CV-D is a potential alternative to standard anthracycline-taxane combination regimens, although further investigations are warranted.

Despite comparable outcomes between CV-D and AC-D in pCR of the primary breast, as well as in the radiological response and breast conservation rates, CV-D appears inferior to AC-D in other efficacy parameters and in the results of subgroup analyses. The rates of pCR in both primary breast and lymph nodes (ypT0/is, ypN0) in patients who received CV-D were about half of those with AC-D (6% vs. 13%), although there were no remarkable differences in the rates of ypT0/is (11% vs. 15%) and ypN0 (44% vs. 39%) between the two arms. Subgroup analyses indicated that no patients with hormone receptor–positive, HER2-negative, and triple-negative breast cancer in the CV-D arm achieved pCR in the primary breast. Given that CV regimens have shown activity across various subgroups in previous studies of metastatic breast cancer [13] and that hormone receptor–positive and HER2-negative tumors are intrinsically less sensitive to neoadjuvant chemotherapy than other subtypes [21-24], this could reflect the small sample size of this trial rather than a lack of efficacy of CV-D in these subgroups.

This study was not designed to show non-inferiority or superiority between two regimens and thus lacked the ability to demonstrate a conclusive difference. Accordingly, it is hard to draw conclusions with regard to the differences in long-term survival outcomes between the two regimens. However, patients assigned to the CV-D arm appear to have worse long-term PFS (5-year PFS rates, 30.2% vs. 51.3%) and OS (5-year OS rates, 61.3% vs. 79.4%) than those in the AC-D arm. Survival curves between the two regimens appeared to be similar until 20 months in PFS and 40 months

in OS, but displayed clear separation after those time points. These findings suggest that CV-D might be inferior for eradication of microscopic metastasis compared to AC-D. On the other hand, the overall efficacy outcomes of our study cohort in both arms appear to be worse than those of other trials investigating neoadjuvant chemotherapy [4,11,25]. This may have occurred because approximately 80% of our patients had locally advanced or inflammatory breast cancer related to worse prognosis than early stage disease.

Both regimens were well tolerated, and safety profiles were consistent with those of previous studies [7,13]. Grade 3-4 neutropenia was the most common severe toxicity of both regimens. Although there was a large difference in the frequency of grade 3-4 neutropenia between first phase AC and CV (80% vs. 47%), this trend was reversed during the second phase docetaxel (74% in the CV-D group vs. 40% in the AC-D group). This discrepancy in severe neutropenia with the same agent indicates the potential delayed toxicity of the CV regimen. However, there was no clear difference in relative dose intensity of docetaxel between the two arms. The high incidence of severe neutropenia in our patients could be attributed to the prohibition of prophylactic administration of colony-stimulating factors. However, this high frequency of neutropenia might be somewhat overestimated because complete blood counts were monitored every week during the first cycle of treatment. In the CV-D arm, diarrhea and hand-foot syndrome were more common than in the AC-D arm. However, most cases were mild and manageable by supportive care.

It should be noted that this study had several limitations. Our study treatments were evaluated in an unselected heterogeneous patient population and anti-HER2 agent was not administered to patients with HER2-positive breast cancer because the role of trastuzumab in the neoadjuvant setting was unclear when this study was designed and started. Although one of the rationales for investigating this non-anthracycline regimen was the potential long-term risk of cardiotoxicity with anthracycline, serial monitoring of cardiac function was not performed in this study. Because neoadjuvant chemotherapy was not widely used in daily practice during the study, more time than expected was spent on patient recruitment, which led to the enrollment of patients with relatively more advanced disease.

Conclusion

Comparable pathological and radiological responses between AC-D and CV-D indicate that CV-D could be a potential candidate for non-anthracycline–based neoadjuvant chemotherapy. Although CV-D may not be generally recommended as neoadjuvant chemotherapy because of the trend for inferior long-term PFS and OS in our study, this regimen may be a reasonable therapeutic option for patients that anthracycline are contraindicated. Further investigations are warranted to clarify the clinical implications of neoadjuvant chemotherapy with CV-D.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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