Comparison of neoadjuvant adriamycin and docetaxel versus adriamycin, cyclophosphamide followed by paclitaxel in patients with operable breast cancer

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Purpose: Neoadjuvant chemotherapy is the standard treatment for patients with locally advanced breast cancer and is increasingly considered for patients with operable disease. Recently, as many clinical trials have demonstrated favorable outcomes of anthracycline–taxane based regimen, this approach has been widely used in the neoadjuvant setting.

Methods: We compared women who received adriamycine and docetaxel (AD) with adriamycin, cyclophosphamide followed by paclitaxel (AC–T) as neoadjuvant chemotherapy. The AD group was scheduled for six cycles of AD (50 mg/m^2 and 75 mg/m^2, respectively) at a 3–week interval. The AC–T group was scheduled for four cycles of adriamycin and cyclophosphamide (50 mg/m^2 and 500 mg/m^2, respectively) followed by four cycles of paclitaxel (175 mg/m^2) at a 3–week interval.

Results: The responses of chemotherapy were equivalent (overall response rate [AD, 75.7% vs. AC–T, 80.9%; P = 0.566], pathologic complete response [pCR] rate [breast and axilla: AD, 10.8% vs. AC–T, 12.8%; P = 1.000; breast only: AD, 18.9% vs. AC–T, 14.9%, P = 0.623], breast conserving surgery rate [P = 0.487], and breast conserving surgery conversion rate [P = 0.562]). The pCR rate in the breast was higher in the human epidermal growth factor receptor 2 (HER2) positive cases (HER2 positive 33.3% vs. negative 10%, P = 0.002). Although nonhematologic toxicities were comparable, hematologic toxicities were more severe in the AD group. Most women in the AD group suffered from grade 3/4 neutropenia (P < 0.001) and neutropenic fever (P < 0.001).

Conclusion: Tumor responses were not different in various variables between the two groups. However, AC–T was a more tolerable regimen than AD in patients with breast cancer receiving neoadjuvant chemotherapy.

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INTRODUCTION

Neoadjuvant chemotherapy (NAC) has become the standard treatment for inoperable cases such as locally advanced and inflammatory breast cancer. In these cases, the use of NAC enables local control after acquirement of respectability by reducing primary tumor size. Recently, NAC has become frequently used in patients with operable, early breast cancer. NAC increases the probability of breast conserving

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surgery (BCS) in patients requiring mastectomy at initial presentation. Furthermore, it permits the rapid assessment of tumor response to a particular chemotherapy regimen. This assessment sometimes provides an opportunity for additional chemotherapy with noncross resistant drugs in patients who fail a first-line regimen [1].

Several prospective clinical trials have been conducted to demonstrate the benefit of NAC, compared to adjuvant chemotherapy [2–5]. Although no survival advantage of NAC over the adjuvant chemotherapy was apparent, NAC was associated with higher rate of BCS, which was directly beneficial to patients because of reduced surgical morbidity and improved body image. In addition, pathologic complete response (pCR) after NAC was remarkable to many clinicians. Although the definition and methods of assessment of pCR varied across the studies, it was one of the primary goals of NAC because the achievement of pCR is a surrogate marker for favorable outcome [2–4]. Several clinical and biological factors are associated with pCR. Among these factors, negative hormone receptor status is widely accepted for predictive marker [6–8].

Several strategies have been introduced to increase pCR and BCS rates. Recently, as several studies demonstrated promising results using taxane in addition to anthracycline [2,9], the non-cross-resistant anthracycline-taxane based regimen has become widely used in clinical practice. In sequential administration of anthracycline and taxane in the neoadjuvant setting, overall response rates and pCR rates were 85% to 93% and 11% to 31%, respectively. In concomitant administration of anthracycline and taxane, overall response rates and pCR rates were 68% to 93% and 8% to 16%, respectively [10]. However, the most effective chemotherapy regimen has not been established and the type of chemotherapy has not been standardized. The current study was conducted to compare the efficacy and tolerability of two anthracycline-taxane based regimens in the neoadjuvant setting.

METHODS

Patients

We performed a retrospective study to analysis the efficacy and safety of NAC. Eligible patients were women aged between 26 and 69 years (mean age, 47 years) with histologically proven breast cancer, who were considered to be candidates for NAC. All patients had adequate performance status (Eastern Cooperative Oncology Group performance status between 0 and 2), adequate hematologic function (hemoglobin, $\geq$10 g/ dL; absolute neutrophil count, $\geq$1,500/mm^3; platelet count, $\geq$ 100,000/mm^3), adequate cardiac function (absence of serious ischemic changes or serious arrhythmias on electrocardiogram or left ventricular ejection fraction $\geq$50% on echocardiogram),

adequate renal function (serum creatinine level $\leq$1.5 mg/dL) and adequate hepatic function (aspartate aminotransferase, alanine aminotransferase, and bilirubin $\leq$1.5 x upper normal limits) confirmed by a pretreatment examination. Patients who were diagnosed systemic metastasis at initial presentation or within 3 months after surgery, who had disease progression during the chemotherapy, who had prior or concomitant malignancy other than breast, who had received any previous treatment for breast cancer, who had active infection or severe concomitant systemic disorder or who discontinued chemotherapy before half cycle of the scheduled regimen were excluded. This study was reviewed and approved by the local Institutional Review Board (AJIRB-MED-MDB-12-168).

Treatment

All patients in this study were received either adriamycin and docetaxel (AD) or adriamycin, cyclophosphamide followed by paclitaxel (AC-T). The AD group was scheduled for six cycles of AD (AD, 50 mg/m^2 and 75 mg/m^2, respectively) at a 3-week interval. The AC-T group was scheduled for four cycles of adriamycin and cyclophosphamide (AC) regimen (AC, 50 mg/m^2 and 500 mg/m^2, respectively) followed by four cycles of paclitaxel 175 mg/m^2 at a 3-week interval. None received hormonal therapy or targeted therapy during NAC. The chemotherapy regimen was randomly selected. Recombinant human granulocyte colony stimulating factor (G-CSF) was not routinely prescribed. However it was allowed by clinical indication.

When the adverse event was not resolved within a week or the event repeated, drug dose was reduced by a maximum of 50% according to the severity. If an adverse event occurred more than three times or if the disease progressed during NAC, chemotherapy was discontinued and the patient underwent immediate surgery. All patients subsequently underwent curative surgery within 5 weeks of the last cycle of chemotherapy.

Assessment

Complete radiologic assessment composed of mammography, breast sonography, and breast magnetic resonance imaging was performed within 3 weeks before the first cycle and after the last cycle of chemotherapy. Bone scan with abdominal sonography or positron emission tomography/ computed tomography was performed before chemotherapy. Physical examination was performed before every cycle of chemotherapy and tumor size was compared. Tumor response was assessed according to the response evaluation criteria in solid tumor version 1.1 [11] as follows. Complete response (CR) was the disappearance of all known lesions. Partial response (PR) was a reduction of more than 30% in the longest

diameter of breast tumor. Stable disease was a reduction of less than 30% or an increase of less than 20%. Progression disease was an increase of more than 20% or the appearance of a new lesion. Toxicities were evaluated at the every cycle of chemotherapy and graded according to common toxicity criteria for adverse events version 3.0.

The diagnosis of breast cancer was performed before chemotherapy by core needle biopsy. Tumor grade and histological type, as well as estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2) status in the immunohistochemistry were confirmed on this procedure. After curative surgery, all specimens were sent to a pathologist and evaluated for pathologic tumor response and adequate tumor staging. If positive margin was reported, re-excision was performed. All cases were finally acquired negative margin. The pCR was defined as the absence of invasive carcinoma in the breast and axillay area, with or without carcinoma in situ. Quasi-pCR was defined as the absence of invasive tumor with only focal residual tumor cells.

Statistical analyses

Each variable was analyzed with IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA) statistical comparison of continuous data (patients' age and tumor size) was performed by Student t-test. Other categorical data including hormone receptor status, histologic grade, response, and toxicity were analyzed by chi-square test or Fisher exact test.

RESULTS

Patient characteristics

Eighty four patients enrolled in present study were treated from 1 January, 2006 to 31 December, 2011. Thirty seven patients received AD and forty seven patients received AC-T. Median age was 47 years (AD group [median, 47 years; range, 26 to 68 years], AC-T group [median, 46 years; range, 27 to 69 years]). Mean clinical tumor size was 3.70 cm (AD, 3.98 ± 2.03 cm; AC-T, 3.49 ± 1.75 cm). The baseline characteristics at the time of initial diagnosis were well balanced between two groups (Table 1). There was no lobular type histology in this study.

Response to chemotherapy

All patients were assessable clinical and pathologic response. One patient received AD regimen experienced disease progression during NAC and this case was excluded from analysis. Tumor response to NAC is summarized in Table 2. The overall response rates were 75.5% (CR, 8.1%; PR, 67.6%) in the AD group and 80.9% (CR, 21.3%; PR, 59.6%) in the AC-T group (P = 0.170). The mean tumor sizes after NAC

Table 1. Baseline characteristics in the AD group and AC-T group

Variable	AD (n = 37)	AC-T (n = 47)	P-value
Age (yr)	47.57 ± 10.31	46.96 ± 9.58	0.780
Menopausal status			0.365
Premenopusal	20 (54.1)	30 (63.8)	
Postmenopausal	17 (45.9)	17 (36.2)	
Tumor size (cm)	3.98 ± 2.03	3.49 ± 1.75	0.236
Clinical stage			0.072
T1	7 (18.9)	11 (23.4)	
T2	18 (48.6)	18 (59.4)	
T3	5 (13.5)	6 (12.8)	
T4	7 (18.9)	2 (4.3)	
Stage II	25 (67.6)	38 (80.9)	0.163
Stage III	12 (32.4)	9 (19.1)	
Estrogen receptor status			0.703
Positive	22 (59.5)	26 (55.3)	
Negative	15 (40.5)	21 (44.7)	
Progesterone receptor status			0.111
Positive	23 (62.2)	21 (44.7)	
Negative	14 (37.8)	26 (55.3)	
HER2 status			0.781
Positive	10 (27.0)	14 (29.8)	
Negative	27 (73.0)	33 (70.2)	
Nuclear grade			0.660
High	16 (61.5)	23 (56.1)	
Low/intermediate	10 (38.5)	18 (43.9)	
Histologic grade			0.109
High	18 (62.1)	17 (42.5)	
Low/intermediate	11 (37.9)	23 (57.5)	
Lymphovascular invasion			0.662
Positive	14 (45.2)	16 (40.0)	
Negative	17 (54.8)	24 (60.0)	
CA15-3 (U/mL)	17.62 ± 24.35	15.00 ± 13.65	0.539

Values are presented as mean ± standard deviation or number (%).
AD, adriamycin and docetaxel; AC-T, adriamycin and cyclophosphamide followed by paclitaxel; HER2, human epidermal growth factor 2; CA15-3, carcinoma agent 15-3.

were 1.93 cm in the AD group and 1.85 cm in the AC-T group, which were markedly reduced in comparison with

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initial clinical tumor size (AD, 3.98 cm; AC–T, 3.49 cm). The pCR rate (both the breast and axilla) was 11.9% (AD, 10.8%; AC–T, 12.8%; P = 1.0). The pCR rate in breast (regardless of axilla) was 16.7% (AD, 18.9%; AC–T, 14.9%; P = 0.623). BCS was performed 67.6% in the AD group and 74.5% in the AC–T group. Among the 48 patients for whom total mastectomy was initially planned, 24 patients (50%) received BCS after NAC. The breast conserving conversion rates in the AD group and AC–T group were 45.5% and 53.3%, respectively (P

= 0.562). The mean clinical tumor size was related with the breast conserving conversion rate (BCS, 3.29 ± 1.14 cm; total mastectomy, 5.73 ± 1.19 cm; P < 0001). No patient required total mastectomy among the case attempted BCS. Table 3 showed chemotherapy response stratified hormonal receptor, HER2 status and triple negative breast cancer. The variables related to tumor response were not different by hormone receptor status. The pCR rates (both the breast and axilla) were 15.6% in the hormone receptor negative group and 9.6% in the hormone receptor positive group (P = 0.409). However, pCR rate in breast was higher in the HER2 positive case (HER2 positive and negative, 33.3% and 10%, respectively; P = 0.002). There were no other factors associated with pCR or breast conserving conversion rate in this study (data not shown).

Table 2. Chemotherapy response

Variable	AD (n = 37)	AC-T (n = 47)	P-value
Clinical response			0.248
Complete response	3 (8.1)	10 (21.3)	
Partial response	25 (67.6)	28 (59.6)	
Stable disease	9 (24.3)	9 (19.1)	
Progression disease	0 (0)	0 (0)	
Overall response	28 (75.7)	38 (80.9)	0.566
Clinical downstage	15 (40.5)	17 (36.2)	0.682
pCR	4 (10.8)	6 (12.8)	1.000
Breast pCR	7 (18.9)	7 (14.9)	0.623
Quasi pCR	11 (29.7)	11 (23.4)	0.513
Breast conserving surgery	25 (67.6)	35 (74.5)	0.487
Breast conserving conversion			0.562
TM → BCS	10 (45.5)	14 (53.8)	
TM → TM	12 (54.5)	12 (46.2)	

Values are presented as number (%).
AD, adriamycin and docetaxel; AC-T, adriamycin and cyclophosphamide followed by paclitaxel; pCR, pathologic complete response; TM, total mastectomy; BCS, breast conserving surgery.

Table 4. Nonhematologic toxicity

Variable	AD (n = 37)	AC-T (n = 47)	P-value
Alopecia[a]	37 (100)	47 (100)	1.000
Hepatic toxicity[b]			
AST	1 (2.7)	2 (4.3)	1.000
ALT	9 (24.3)	8 (17.0)	0.408
Bilirubin	1 (2.7)	0 (0)	0.440
Neuase/vomitting[b]	7 (18.9)	7 (14.9)	0.623
Diarrhea[b]	5 (13.5)	3 (6.4)	0.292
Mucositis[b]	4 (10.8)	2 (4.3)	0.398
Neuropathy[b]	1 (2.7)	6 (12.8)	0.128

Values are presented as number (%).
AD, adriamycin and docetaxel; AC-T, adriamycin and cyclophosphamide followed by paclitaxel; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a]Over grade 1. [b]Over grade 2.

Table 3. Chemotherapy response stratified hormonal receptor, HER2 status and triple negative breast cancer

Variable	Hormone receptor status			HER2 status			Triple negative breast cancer		
	HR (-) (n = 32)	HR (+) (n = 52)	P-value	HER2 (-) (n = 60)	HER2 (+) (n = 24)	P-value	TN (n = 16)	Non-TN (n = 68)	P-value
Overall response (66 cases)	23 (71.9)	43 (82.7)	0.241				15 (93.8)	51 (75.0)	0.343
pCR (10 cases)	5 (15.6)	5 (9.6)	0.409	5 (8.3)	5 (20.8)	0.140	3 (18.8)	7 (10.3)	0.415
Breast pCR (14 cases)	8 (25.0)	6 (11.5)	0.108	6 (10.0)	8 (33.3)	0.020	3 (18.8)	11 (16.2)	1.000
Quasi-pCR (22 cases)	10 (31.3)	12 (23.0)	0.408	12 (20.0)	10 (41.7)	0.041	3 (18.8)	19 (27.9)	0.539
Breast conserving conversion									
TM → BCS (24 cases)	11 (55.0)	13 (46.4)	0.558	15 (25.0)	9 (37.5)	0.263	6 (60)	18 (47.4)	0.477
TM → TM (24 cases)	9 (45.0)	15 (53.6)		16 (26.7)	8 (33.3)		4 (40)	20 (52.6)	

Values are presented as number (%).
HER2, human epidermal growth factor 2; HR, hormone receptor; TN, triple negative; pCR, pathologic complete response; TM, total mastectomy; BCS, breast conserving surgery.

Table 5. Hematologic toxicity

Variable	AD (n = 37)	AC-T (n = 47)	P-value
Neutropenia[a]	37 (100)	13 (27.7)	<0.001
Neutropenic fever	21 (56.8)	1 (2.1)	<0.001
Anemia[a]	6 (16.2)	1 (2.1)	0.400
Thrombocytopenia[a]	0 (0)	1 (2.1)	1.000

Values are presented as number (%).
AD, adriamycin and docetaxel; AC-T, adriamycin and cyclophosphamide followed by paclitax.
[a]Over grade 3.

Tolerability

There were no mortality cases during the NAC. Nonhematologic toxicities over grade 2 were uncommon (hepatic toxicities, 20.2%; nausea/vomiting, 16.7%; diarrhea, 9.5%; neuropathy, 8.3%; and mucositis, 7.1%) and there were no differences between the two groups (Table 4). Cardiac adverse events did not occur in any patient. No patient changed the planned schedule or dose due to nonhematologic toxicities. However, hematologic toxicities had a more severe tendency in the AD group (Table 5). All patients in the AD group experienced grade 3/4 neutropenia, whereas 13 of 47 patients (27.7%) in the AC–T group experienced grade 3/4 neutropenia (P < 0.001). In addition, neutropenic fever occurred in 56.8% and 2.1% in the AD group and AC–T group, respectively (P < 0.001). Although more patients experienced grade 3/4 anemia in the AD group, there were no statistical differences (P = 0.40). No patient required erythropoietin or blood transfusion due to anemia.

DISCUSSION

Recently, NAC has become one of the treatment options for early breast cancer in addition to its traditional role for inflammatory or inoperable breast cancer. A number of clinical trials have showed the role of NAC for operable and early breast cancer. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B–18 trial [4], women with operable breast cancer receiving four cycles of AC were randomly assigned to either neoadjuvant or adjuvant chemotherapy group. The differences in overall survival, disease free survival or ipsilateral breast tumor recurrence (IBTR) rate were not evident between the two groups. In the group receiving NAC, the pCR rate was 13% and the BCS rate was significantly higher, compared to the group receiving adjuvant chemotherapy (67% vs. 60%, respectively; P = 0.002). At follow-up, patients with a pCR had higher overall survival and disease free survival rate than patients with residual disease. The women in the NSABP B–27 trial [2,3] were randomly assigned to neoadjuvant AC alone, to neoadjuvant AC followed by decetaxel (AC–D), or to neoadjuvant AC followed by adjuvant docetaxel. The addition of preoperative docetaxel improved the pCR rate (13.7% in the preoperative AC arm vs. 26.1% in the preoperative AC–D arm, P < 0.001) and the overall clinical response rate (85.5% vs. 90.7%, respectively; P < 0.001). The achievement of pCR was a significant predictor of survival, irrespective of treatment (hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.23 to 0.47; P < 0.0001). However, the addition of docetaxel in the preoperative or postoperative setting after AC did not improve the long-term outcome in this study, although the addition of taxane in other study conducted in the adjuvant setting showed significant survival gain (absolute benefit of 2.0–2.8%) [12]. In the German Preoperative Adriamycin Docetaxel (GeparDuo) trial [9], women were randomized to either four cycles of AC followed by four cycles of docetaxel at a 3–weeks interval (AC–DOC) or four cycles of doxorubicin and docetaxel with G–CSF support at a 2–week interval (ADOC). The study demonstrated superior response rates after sequential administration of docetaxel. The pCR rates in the breast were 14.3% for AC–DOC and 7.0% for ADOC (P < 0.001) and the response rates were 78.6% for AC–DOC and 68.6% for ADOC (P < 0.001).

In our study, we compared women receiving AD with those receiving AC–T, which was similar to GeparDuo trial in terms of comparison of two kinds of anthracycle–taxane based regimen (AD vs. AC–T in our study and ADOC vs. AC–DOC in GeparDuo trial). However, the patients' baseline characteristics and planned schedule of chemotherapy were different. The patients in ADOC were received 4 cycles of AD at the 2–week interval and the AD group in our study was received 6 cycles of same drug at the 3–week interval. Another arm of each study used different taxane agent (docetaxel in GeparDuo trial and paclitaxel in our study) with different dosage (AC were 60 mg/m^2 and 600 mg/m^2 in AC–DOC and 50 mg/m^2 and 500 mg/m^2 in AC–T group, respectively). When we compared the results of two studies, our study was higher pCR in AD group than ADOC and lower in AC–T group than AC–DOC (pCR rates were 10.8% and 12.6% in the AD and AC–T, respectively and 7.0% and 14.3% in ADOC and AC–DOC, respectively). Although the correlation was not evidently, the results in two studies seem to be associated with cycle and dosage. In GeparDuo trial, AC–DOC was higher response rate than ADOC. However, in our study, responses of two groups (AD vs. AC–T) were equivalent. A research compared docetaxel versus paclitaxel with anthracycline and cyclophosphamide [13]. In this research, the regimen of docetaxel with anthracycline and cyclophosphamide offered a better outcome. However more research is needed to determine the superiority of two taxane regimens. Other trials

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using anthracycle–taxane based regimens as NAC have shown varied response rates (pCR rates ranged from 15% to 26%) [14–17]. It was thought that this differences between the studies arose from the variety of the heterogeneous group, different response profile of breast cancer, and the different definition of chemotherapy response including pCR.

The definition of pCR was not uniform across the trials and assessment methods were not standardized, although achievement of pCR is known to be a surrogate marker of improved long–term outcomes, regardless of the type of chemotherapy [2–4]. Some defined a pCR as the absence of invasive tumor cell in the breast, regardless of noninvasive tumor cell [3,4], but others strictly defined it as the absence of invasive and noninvasive tumor cell in the breast and axilla [9]. Indeed, the pCR rates were diverse according to the definition, irrespective of the efficacy of the particular regimen. We adopted a pCR definition of the absence of invasive tumor cells in the breast and axilla because the presence of *in situ* lesions does not impact long–term outcomes [18] and the absence of axillary lymph node after NAC is a strong pre-dictor of improved prognosis [19]. However, we adopted another definition of pCR (pCR in breast), which has been most widely accepted including in the NSABP B–18 and B–27 trials. We expected to show a more distinct difference of efficacy between the arms by this definition, but could not demonstrate statistical significance. We also analyzed predicting factors of pCR. It is known that predictive mar-kers of pCR include negative hormone receptor status, triple negative breast cancer, HER2 positive status, small tumor size, nonlobular histology, high Ki–67, high grade and lymph–ovascular invasion. Of these factors, negative hormone re-ceptor status was the most acceptable marker for response to NAC in various studies [6–8]. Although, in our study, hormonal receptor status did not reach statistical significancy, HER2 overexpression was related with pCR (HER2 positive and negative, 33.3% and 10%, respectively; P = 0.002). Two studies which were performed with same population also demonstrated that HER2 overexpression was a surrogate marker predicting pCR [7,20]. It is known that HER2 encodes a transmembrane tyrosine kinase active protein, which is a component of the epidermal growth factor receptor family. It influences cell proliferation and differentiation by signal transduction and relates with poor prognosis. Although there has been a controversy about the HER2 status in relation to response to chemotherapy, many researchers demonstrated that HER2 overexpression was a biomarker predicting pCR [7,20–22]. They explained that HER2 overexpression was related to sensitivity of anthracycline. HER2 was often co-amplified with topoisomerase IIa which was located at chro-mosome 17, close to the *HER2* gene. These genes played a

role in the target and mediator of anthracycline–induced cytotoxicity [21,22]. However, the clear mechanism has not been established and more research should be necessary

Another primary end point in our study was BCS rate and BCS conversion rate in patients for whom total mastectomy had been initially planned. BCS rates were 67.6% and 74.5% in the AD groups and AC–T groups, respectively (P = 0.487), which was comparable to previous trials [2–4,9]. BCS conversion rates were 45.5% and 53.8% in the AD groups and AC–T groups, respectively (P = 0.562), which was higher than that of other studies [4,23]. However, BCS after NAC for women initially suitable total mastectomy had conflicting results across the studies. Some researchers resulted in a worse prognosis in patients receiving BCS after NAC [24]. Buchholz et al. [25] suggested that the response pattern of breast cancer after NAC is heterogeneous. One type of regression was concentric shrinkage and another was patch regression, leaving scattered tumor cells. In the latter pattern, BCS had a risk for microscopic disease. In a meta–analysis of 11 studies [23], BCS rates after NAC increased significantly, although more patients had an IBTR in the NAC group. However, when three studies in which the patients achieving complete clinical response received only radiotherapy for local control were excluded, there was no differences between two groups (HR, 1.12; 95% CI, 0.92 to 1.37). In the NSABP B–18 trial, IBTR was observed in 15.9% of women receiving BCS initially suitable for mastectomy, whereas 9.9% of women eligible for BCS at initial diagnosis had IBTR. However, after correction of age, there was no difference between the two groups. In our study, 50% patients received BCS after NAC were initially eligible for total mastectomy. Nevertheless, there have been no IBTR cases, although systemic recurrence and regional nodal recurrence occurred in six and five women, respectively. However, we could not demonstrate the result of long–term follow–up data, because half of the patients were enrolled within 18 months and this period did not have statistical power. A long–term follow–up will be necessary to demonstrate definite prognostic difference in regard to NAC.

Our data indicate that more hematologic toxicities occurred in the AD group, whereas the response to chemotherapy and nonhematologic toxicity were equivalent. Most patients in the AD group suffered from grade 3/4 neutropenia and neutropenic fever. The detection rate of hematologic toxities in the AD group was somewhat higher than other studies using a similar regimen [7,9,26]. However, patient characteristics differed between the studies and other studies reported the toxicity rate as the percent of observation cycles among the total cycles. Presently, we demonstrated the percent of occurred patients among total patients. Furthermore, we did not permit G–CSF routinely and performed a strict evaluation

by our institutional policy. So a direct comparison with other studies was difficult and not reasonable.

In conclusion, AC-T regimen is similar in efficacy, compared to AD regimen. The overall response rate, pCR rate, and BCS rate are not different. However, the AC-T regimen is more tolerable than the AD regimen with regard to hematologic toxicities. No relating factor to predict pCR was available in this study.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. von Minckwitz G, Kummel S, Vogel P, Hanusch C, Eidtmann H, Hilfrich J, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008;100:552-62.

2. Bear HD, Anderson S, Smith RE, Geyer CE Jr, Mamounas EP, Fisher B, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006;24:2019-27.

3. Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, 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.

4. Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. Cancer 2002;95:681-95.

5. Cuppone F, Bria E, Carlini P, Milella M, Felici A, Sperduti I, et al. Taxanes as primary chemotherapy for early breast cancer: meta-analysis of randomized trials. Cancer 2008;113:238-46.

6. Kaufmann M, von Minckwitz G, Bear HD, Buzdar A, McGale P, Bonnefoi H, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007;18:1927-34.

7. Gwak G, Kim JY, Park K, Shin YJ, Cho H, Park SJ, et al. Comparison of Doxorubicin plus docetaxel neoadjuvant chemotherapy with Doxorubicin plus vinorelbine in primary breast cancer. J Breast Cancer 2011;14:129-34.

8. Jones RL, Salter J, A'Hern R, Nerurkar A, Parton M, Reis-Filho JS, et al. Relationship between oestrogen receptor status and proliferation in predicting response and long-term outcome to neoadjuvant chemotherapy for breast cancer. Breast Cancer Res Treat 2010;119:315-23.

9. von Minckwitz G, Raab G, Caputo A, Schutte M, Hilfrich J, Blohmer JU, 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 GEPARDUO study of the German Breast Group. J Clin Oncol 2005;23:2676-85.

10. Gradishar WJ, Wedam SB, Jahanzeb M, Erban J, Limentani SA, Tsai KT, et al. Neoadjuvant docetaxel followed by adjuvant doxorubicin and cyclophosphamide in patients with stage III breast cancer. Ann Oncol 2005;16:1297-304.

11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

12. Bria E, Nistico C, Cuppone F, Carlini P, Ciccarese M, Milella M, et al. Benefit of taxanes as adjuvant chemotherapy for early breast cancer: pooled analysis of 15,500 patients. Cancer 2006;106:2337-44.

13. Su J, Li MQ, Xu H, Hu D. Clinical comparative study of neoadjuvant chemotherapy outcome in locally advanced breast cancer: docetaxel versus paclitaxel plus pirarubicin hydrochloride and cyclophosphamide. Zhonghua Yi Xue Za Zhi 2011;91:1837-9.

14. Malhotra V, Dorr VJ, Lyss AP, Anderson CM, Westgate S, Reynolds M, et al. Neoadjuvant and adjuvant chemotherapy with doxorubicin and docetaxel in locally advanced breast cancer. Clin Breast Cancer 2004;5:377-84.

15. Espinosa E, Morales S, Borrega P, Casas A, Madroñal C, Machengs I, et al. Docetaxel and high-dose epirubicin as neoadjuvant chemotherapy in locally advanced breast cancer. Cancer Chemother Pharmacol 2004;54:546-52.

16. Schneeweiss A, Huober J, Sinn HP, von Fournier D, Rudlowski C, Beldermann F, et al. Gemcitabine, epirubicin and docetaxel as primary systemic therapy in patients with early breast cancer: results of a multicentre phase I/II study. Eur J Cancer 2004;40:2432-8.

17. Conte PF, Donati S, Gennari A, Guarneri V, Orlandini C, Rondini M, et al. Primary chemotherapy with gemcitabine, epirubicin and taxol (GET) in operable breast cancer: a phase II study. Br J Cancer 2005;93:406-11.

18. Mazouni C, Peintinger F, Wan-Kau S, Andre F, Gonzalez-Angulo AM, Symmans WF, et al. Residual ductal carcinoma in situ in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. J Clin Oncol 2007;25:2650-5.

19. Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. J Clin Oncol 2005;23:9304-11.

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20. Kim JW, Jung SK, Eum T, Koo BY, Kang HJ, Kim LS. Pathologic findings of residual tumor according to the response rate after neoadjuvant chemotherapy for breast cancer. J Korean Surg Soc 2008;75:1-8.

21. Andre F, Mazouni C, Liedtke C, Kau SW, Frye D, Green M, et al. HER2 expression and efficacy of preoperative paclitaxel/FAC chemotherapy in breast cancer. Breast Cancer Res Treat 2008;108:183-90.

22. Wang L, Jiang Z, Sui M, Shen J, Xu C, Fan W. The potential biomarkers in predicting pathologic response of breast cancer to three different chemotherapy regimens: a case control study. BMC Cancer 2009;9:226.

23. Mieog JS, van der Hage JA, van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. Br J Surg 2007;94:1189-200.

24. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005;97:188-94.

25. Buchholz TA, Lehman CD, Harris JR, Pockaj BA, Khouri N, Hylton NF, et al. Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: a National Cancer Institute conference. J Clin Oncol 2008;26:791-7.

26. Han S, Kim SB, Kang SS, Noh WC, Paik NS, Chang ES, et al. A phase II study of neoadjuvant docetaxel plus doxorubicin (KBCS-01) in stage II, III breast cancer. Breast Cancer Res Treat 2006;98:57-61.