Journal of Breast Cancer

J Breast Cancer 2017 December; 20(4): 340-346 https://doi.org/10.4048/jbc.2017.20.4.340

Check for updates

ORIGINAL ARTICLE

A Multicenter Phase II Trial of Neoadjuvant Chemotherapy with Docetaxel and Gemcitabine in Locally Advanced Breast Cancer

Ye Won Jeon, Tae Hyun Kim[1], Hyun Jo Youn[2], Sehwan Han[3], Yongsik Jung[3], Geumhee Gwak[4], Young Sam Park[5], Jeong Soo Kim[6], Young Jin Suh

Department of Surgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon; [1]Department of Surgery, Inje University Busan Paik Hospital, Busan; [2]Department of Surgery, Chonbuk National University Hospital, Jeonju; [3]Department of Surgery, Ajou University School of Medicine, Suwon; [4]Department of Surgery, Inje University Sanggye Paik Hospital, Seoul; [5]Department of Surgery, Presbyterian Medical Center, Jeonju; [6]Department of Surgery, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, Korea

Purpose: The current multicenter phase II study was conducted to evaluate the efficacy and safety of the combination of docetaxel and gemcitabine as neoadjuvant chemotherapy (NAC) for locally advanced breast cancer. **Methods:** A total of 98 patients with stage II–III breast cancer were enrolled. The primary endpoint was pathological complete response (pCR) rate of invasive cancer after the completion of the fourth cycle of NAC. The secondary endpoints included response rate (RR), rate of breast-conserving surgery, toxicity, and disease-free survival (DFS). This study is registered with ClinicalTrials.gov (NCT01352494). **Results:** pCR in the breast and the axillary lymph node was observed in seven of the 98 enrolled patients (7.1%). The overall clinical RR, including partial responses, was 65.3%. Breast-conserving surgery was performed in 75 of the 98 assessable patients (76.5%). Neutropenia was frequent and was observed in 92 of the 98 patients (93.9%), including grade 3 and 4 in 24 patients (24.5%) and 63 patients (64.3%), respectively. Dose reductions were required for 30 of the 92 patients (32.6%). After a median follow-up of 24 months, the overall DFS of the group was 86.7%. **Conclusion:** The combination of docetaxel and gemcitabine did not improve pCR. However, this regimen has shown potential as a NAC by producing a reasonable rate of breast-conserving surgery and favorable responses in patients with locally advanced breast cancer. The therapeutic efficacy of this regimen will be determined in additional trials to overcome the limitations of the current study.

Key Words: *Breast neoplasms, Docetaxel, Gemcitabine, Neoadjuvant therapy*

INTRODUCTION

Neoadjuvant chemotherapy (NAC) is a well-established standard treatment option for patients with large and locally advanced breast cancer, which has poor prognosis and a high risk of distant metastasis [1,2]. In this context, the purpose of NAC is to not only downsize a primary tumor to help conserve breast tissue but also to improve clinical outcome by eliminating micrometastases. Furthermore, NAC can be used as an *in vivo* chemosensitivity test, allowing rapid evaluation of an individual regimen [2-4]. Although a survival benefit has not been demonstrated when comparing NAC to adjuvant chemotherapy, the pathologic complete response (pCR) rates documented in several NAC studies are predictive of favorable long-term outcomes and indicate the potential of pCR as a surrogate marker for survival [1,5].

Anthracycline- and taxane-based chemotherapy remains the primary option for most neoadjuvant and adjuvant chemotherapy regimens for locally advanced breast cancer. However, because cardiotoxicity has been associated with anthracycline-based chemotherapy, studies assessing taxane-based and combination chemotherapy regimens (such as those using capecitabine, vinorelbine, and cyclophosphamide) that can be an alternative to anthracycline-based regimens have been conducted [6-11]. The safety and efficacy of gemcitabine (2′,2′-difluorodeoxycytidine), a nucleoside analogue anti-metabolite, as monotherapy for advanced breast cancer has been

Correspondence to: **Young Jin Suh**
Department of Surgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 16247, Korea
Tel: +82-31-249-8169, Fax: +82-31-247-5347
E-mail: yjsuh@catholic.ac.kr

This investigator-initiated clinical trial was supported by Yuhan Pharmaceutical Co. (KBCSG009).

The abstract was selected for presentation as part of the treatment at the Global Breast Cancer Conference 2016 in Korea.

Received: June 26, 2017 **Accepted:** November 7, 2017

established [11]. The objective response rate (RR) of a combination treatment of docetaxel and gemcitabine ranged from 30% to 58% [7,9,10,12]. Furthermore, this combination was effective in patients with anthracycline-pretreated metastatic disease without excessive toxicity [6,10].

Based on these reports, the combination of docetaxel and gemcitabine may offer a new NAC regimen for locally advanced stage II–III breast cancer. However, reports on NAC using the combination treatment of docetaxel and gemcitabine are limited [13,14]. Therefore, we aimed to assess the efficacy and safety of the combination of docetaxel and gemcitabine as NAC in the current multicenter, single-arm, phase II study in women with locally advanced stage II–III breast cancer.

METHODS

Eligibility criteria

This study was a phase II, multicenter, single-arm trial involving six institutions in Korea. Patients with pathologically confirmed locally advanced clinical stage II–III primary breast cancer were eligible for inclusion. The other eligibility criteria included age between 20 and 70 years; no prior chemotherapy, hormonal therapy, or radiotherapy for breast cancer or other invasive cancer; and an Eastern Cooperative Oncology Group performance status of 0 to 2. Eligible patients were required to have adequate hematologic (hemoglobin, ≥ 9.0 g/dL; absolute neutrophil count, $\geq 1{,}500/\mu L$; and platelets $\geq 100 \times 10^3/\mu L$), neurologic, hepatic (aspartate transaminase [AST], alanine transaminase [ALT], and alkaline phosphatase all ≤ 1.5 times the upper limit of normal and bilirubin within normal limits), renal (serum creatinine within normal limits), and cardiac function. Patients with inflammatory or metastatic breast cancer were excluded.

All tumors were tested locally for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status. The cutoffs for ER and PR positivity were $>1\%$ positively stained tumor cells on immunohistochemistry (IHC). Hormone receptor (HR) status was classified as positive or negative for ER and/or PR. Tumor HER2 status was determined using IHC and/or fluorescence *in situ* hybridization (FISH) analysis, and HER2+ tumors were defined according to an IHC score of 3+ or gene amplification using FISH.

The local ethics committee or Institutional Review Board at each institution approved the study (VC11MCMS0163). All patients gave written informed consent to participate. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. This study is registered with ClinicalTrials.gov (NCT01352494).

Treatment

The patients were intravenously administered docetaxel (Doxotel®; Yuhan, Seoul, Korea) at a dose of 75 mg/m^2 over 60 minutes on day 1 and gemcitabine (Gemcibine®; Yuhan) at a dose of 1,000 mg/m^2 over 30 minutes on days 1 and 8 in four cycles of 21 days each. The patients were orally premedicated with 8 mg dexamethasone at 12, 8, and 1 hour prior to docetaxel infusion and were continued on dexamethasone 8 mg twice a day through the next day (for a total of 6 times). Prophylactic anti-emetics were administered according to the protocol of each participating institution.

In case of grade 4 neutropenia or febrile neutropenia, recombinant granulocyte-colony stimulating factor (G-CSF) was administered during the subsequent cycles. Furthermore, the doses of docetaxel and gemcitabine were reduced by one dose level in the next cycle. If grade 3 neutropenia occurred, the doses of docetaxel and gemcitabine were reduced after the second event. The doses of docetaxel and gemcitabine were initially reduced to 60 mg/m^2 and 750 mg/m^2, respectively. A second dose reduction to 45 mg/m^2 docetaxel and 500 mg/m^2 gemcitabine was allowed if severe adverse events still occurred after the first dose reduction.

Surgery was performed after the completion of the four cycles of NAC, preferably within 6 weeks. The choice of definitive curative surgery depended on the surgeon's discretion. Pathologists reviewed the operative specimens for pathologic response at each participating institution. Thereafter, the patients received curative surgery followed by adjuvant chemotherapy according to the physician's decision, considering the response to NAC and final pathologic stage. The patients who underwent breast-conserving surgery received radiotherapy to the whole breast with a boost to the primary site. Post-mastectomy radiotherapy was recommended for patients who had at least clinical stage III disease or a clinical tumor size ≥ 5 cm at diagnosis as well as the pathological involvement of ≥ 4 axillary lymph nodes. Endocrine therapy after surgery was required for HR-positive patients for a minimum of 5 years, and the choice of agents was determined by the investigator. Patients with HER2+ disease continued trastuzumab at tri-weekly intervals for 1 year.

Assessments

The clinical tumor response was assessed after the completion of the second/fourth cycle of NAC and before surgery. Response assessment was evaluated using computed tomography and/or magnetic resonance imaging in accordance with the modified Response Evaluation Criteria in Solid Tumors

guidelines (version 1.1). pCR was defined as no residual invasive cancer component within a primary breast lesion and axillary lymph nodes after NAC and only ductal carcinoma *in situ* present after NAC (defined as ypT0/is ypN0). Laboratory and non-laboratory toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. Toxicity was evaluated in all patients who received at least one dose of study therapy.

Statistical analysis

The primary endpoint was pCR rate. A Simon's two-stage optimal design was used to estimate the appropriated sample size. The following hypothesis was to be tested: H_0:c < 10% versus H_1:c > 20%, where c is pCR rate. If the pCR rate was ≤ 10%, the regimen was not suitable for further studies. If the pCR rate was > 20%, the regimen was suitable for further studies. The target alpha level (probability of the wrong positive decision to continue with a low pCR rate [< 10%]) was set at 5%. The target beta level (probability of the wrong negative decision to stop with a pCR [> 20%]) was set at 20%, corresponding to a power of 90%. An initial cohort of 30 patients was scheduled to be enrolled. If four objective responses were achieved in the first 30 patients, 59 additional patients were scheduled to be enrolled during the second part of the trial.

The secondary endpoints included clinical RR, rate of breast-conserving surgery, toxicity, and disease-free survival (DFS). The pCR rates and clinical RRs were calculated with 95% confidence intervals (CIs), with each complete RR based on a binominal distribution. DFS was calculated as the time from neoadjuvant treatment to diagnosis of a recurrent disease in the ipsilateral breast or at a local, regional, or distant site. Survival curves were estimated using the Kaplan-Meier method. A *p*-value of less than 0.05 was considered significant. All analyses were performed using SPSS software version 18.0.1 (SPSS Inc., Chicago, USA).

RESULTS

Patient characteristics

From January 2012 through August 2013, 98 patients with stage II–III breast cancer who met the eligibility criteria were enrolled in the study. Baseline demographic data and clinical patient characteristics are summarized in Table 1. The median age was 42 years (range, 17–70 years). The clinical stage distribution is as follows: 44 patients (44.9%) with stage IIA disease, 27 patients (27.6%) with stage IIB disease, 14 patients (14.3%) with stage IIIA disease, seven patients (7.1%) with stage IIIB disease, and six patients (6.1%) with stage IIIC disease. Fifty patients (51.0%) had HR+/HER2– subtype; 16 patients (16.3%), HR+/HER2+ subtype; 15 patients (15.3%), HR–/HER2+ subtype; and 17 patients (17.4%), HR–/HER2– subtype.

Table 1. Demographic and tumor data (n = 98)

Characteristic	No. (%)
Age (yr)*	42 (21–70)
Performance status	
ECOG 0	83 (84.7)
ECOG 1	15 (15.3)
Menopausal status	
Premenopause	49 (50)
Postmenopause	49 (50)
Tumor stage	
cT1	6 (6.1)
cT2	67 (68.4)
cT3	15 (15.3)
cT4	10 (10.2)
Axillary lymph node status	
cN0	41 (41.9)
cN1	40 (40.8)
cN2	11 (11.2)
cN3	6 (6.1)
TNM stage	
cIIA	44 (44.9)
cIIB	27 (27.6)
cIIIA	14 (14.3)
cIIIB	7 (7.1)
cIIIC	6 (6.1)
Histologic type	
Ductal	87 (88.8)
Mucinous	5 (5.1)
Medullar	1 (1.0)
Other	5 (5.1)
Hormonal receptor expression	
ER (+)/PR (+)	43 (43.9)
ER (+)/PR (–)	23 (23.5)
ER (–)/PR (–)	32 (32.6)
HER2 expression	
Negative	67 (68.4)
Positive	31 (31.6)
Histologic grade	
Low (grade 1)	25 (25.3)
Intermediate (grade 2)	56 (57.1)
High (grade 3)	17 (17.3)

ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.
*Median (range).

Compliance and adverse events

Ninety-eight patients were started in the protocol therapy; of them, 89 patients (90.8%) completed four cycles of docetaxel and gemcitabine. Nine patients proceeded to surgical resection after two cycles of docetaxel and gemcitabine. Of these patients, two discontinued NAC because of radiological com-

https://doi.org/10.4048/jbc.2017.20.4.340

Table 2. Treatment-related adverse events

Toxicity	Grade 1–2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Hematological			
Neutropenia	5 (5.1)	24 (24.5)	63 (64.3)
Febrile neutropenia	-	7 (7.1)	3 (3.1)
Thrombocytopenia	3 (3.1)	-	-
Anemia	8 (8.2)	-	-
Nonhematological			
Fatigue	50 (51.0)	3 (3.1)	-
Stomatitis/mucositis	11 (11.2)	1 (1.0)	-
Fluid retention	23 (23.5)	5 (5.1)	-
Diarrhea	10 (10.2)	-	-
Abdominal pain	3 (3.1)	-	-
AST/ALT elevation	30 (30.6)	6 (6.1)	-
Nausea	8 (8.2)	-	-
Vomiting	2 (2.0)	-	-
Rash	9 (9.2)	3 (3.1)	-
Nail disorders	7 (7.1)	-	-
Pain	12 (12.2)	2 (2.0)	-
Infection	7 (7.1)	-	-
Peripheral sensory neuropathy	8 (8.2)	-	-

AST = aspartate transaminase; ALT = alanine transaminase.

plete response, two discontinued NAC because of severe adverse event from docetaxel and gemcitabine, and five discontinued NAC because of radiological progression or stable disease.

All patients were evaluable for toxicity. The grade 1 to 4 adverse events that occurred in the patients during the docetaxel and gemcitabine treatment are listed in Table 2. During the docetaxel and gemcitabine treatment, the most frequent hematological toxicity was neutropenia. Neutropenia was observed in 92 of the 98 patients (93.9%), including grade 3 and 4 in 24 (24.5%) and 63 patients (64.3%), respectively. Grade 4 febrile neutropenia occurred in three patients (3.1%); they were admitted to the hospital for IV antibiotics and G-CSF support and later discharged uneventfully. Dose reductions were required for 30 of the 92 patients (32.6%). A second dose reduction was required for only one patient. No grade 3 and 4 thrombocytopenia and anemia occurred. The most common nonhematological toxicities included fatigue (51.0%), AST/ALT elevation (30.6%), fluid retention (23.5%), pain (12.2%), stomatitis/mucositis (11.2%), and diarrhea (10.2%). No grade 4 nonhematological toxicity or toxic death was recorded. No treatment-related deaths occurred.

Efficacy and survival

All 98 patients underwent surgical resection after NAC and were evaluable for study outcomes. Breast-conserving surgery was performed on 75 of the 98 assessable patients (76.5%).

Table 3. Pathological complete response rates according to molecular subtypes

Subtypes	ypT0/is No. (%)	ypN0 No. (%)	pCR (ypT0/is ypN0) No. (%)
HR(+)/HER2(–)	6/50 (12.0)	8/29 (27.6)	2/50 (4.0)
HR(+)/HER2(+)	4/16 (25.0)	4/11 (36.4)	4/16 (25.0)
HR(–)/HER2(+)	2/15 (13.3)	1/8 (12.5)	1/15 (6.7)
HR(–)/HER2(–)	1/17 (5.9)	3/9 (33.3)	0/17 (0)
Total	13/98 (13.3)	16/57 (28.1)	7/98 (7.1)

pCR = pathologic complete response; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.

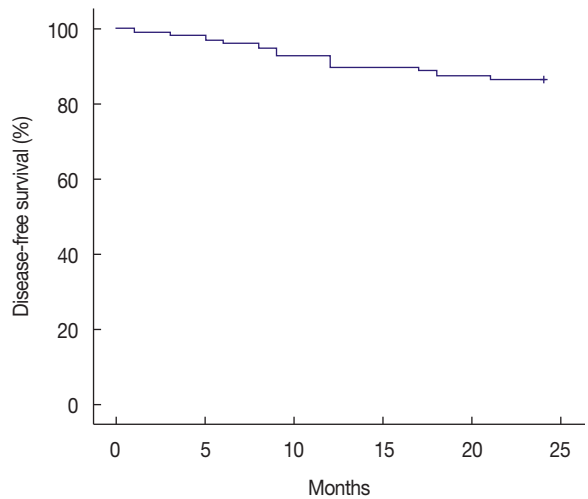

Figure 1. Kaplan-Meier curves showing the disease-free survival of all patients (n = 98).

The pCR rates are shown in Table 3. A pCR (ypT0/is ypN0) in the breast and axillary lymph nodes was observed in seven of the 98 patients (7.1%; 95% CI, 2.1–12.2), which met the primary endpoint of this study. The ypT0/is rate in the breast was 13 of the 98 patients (13.3%), and the ypN0 rate was 16 of the 57 patients (28.1%) in proven axillary lymph node metastasis.

The pCR rates in the breast and axillary lymph nodes according to HR and HER2 status were 4.0% (2/50) in patients with HR+/HER2– subtype, 25.0% (4/16) in patients with HR+/HER2+ subtype, 6.7% (1/15) in patients with HR–/HER2+ subtype, and 0% in patients with HR–/HER2– subtype. Furthermore, patients with HER2-positive malignancy achieved a higher pCR than those with HER2-negative tumors (16.1% vs. 3.0%, $p = 0.031$); however, no significant difference was observed in pCR between the patients with HR-positive tumors and HR-negative tumors (9.1% vs. 3.1%, $p = 0.266$).

The overall clinical RR was 65.3% (64/98; 95% CI, 55.8–

74.8), including clinical complete responses in nine patients (9.2%) and partial responses in 55 patients (56.1%). A total of 32 patients (32.7%) achieved clinically stable disease, while progressive disease was recognized in two patients (2.0%). Similar to the pCR rates, patients with HER2-positive tumors (25/31, 80.65%) achieved a higher overall clinical RR than those with HER2-negative tumors (39/67, 58.2%) ($p = 0.024$).

After a median follow-up of 24 months, the DFS was 87% (95% CI, 78.1–95.9) (Figure 1). At the time of analysis, 13 patients (13.3%) had relapsed. A total of three, six, and four patients had local, distant, and both local and distant relapse, respectively. Although the patients with HER2-positive tumors achieved higher pCR rates and overall clinical RRs compared to those with the HER2-negative tumors, no significant difference was observed in DFS between the two tumor types ($p = 0.079$).

DISCUSSION

In large and locally advanced breast cancer, NAC is performed to shrink the primary tumor to facilitate breast-conserving procedures and to evaluate sensitivity to chemotherapy [2-4]. The pCR after NAC has potential as a surrogate marker for survival [1,5]. As the core of most neoadjuvant and adjuvant chemotherapy regimens for locally advanced breast cancer, the pCR after four cycles of anthracycline-based NAC ranges from 6% to 13% [3,15,16], whereas this increases to 8.0%–26.0% when a combination of anthracycline and taxane NAC is adopted [15,16]. However, both NAC regimens are not always used to treat all locally advanced stage II–III breast cancers. Although the efficacy of anthracycline-based chemotherapy has been well established, the development of cardiotoxicity as a late adverse event is often problematic and serious. This outcome has led to the investigation and development of combination therapies using non-anthracycline and taxane regimens.

Gemcitabine is effective in various solid tumors, including breast cancer, where it has been investigated both as monotherapy and combination therapy. Gemcitabine monotherapy has been proven to be effective and safe in patients with metastatic breast cancer. The RRs in phase II studies that enrolled more than 300 patients ranged from 14% to 42% [11,17-20]. The combination of docetaxel and gemcitabine chemotherapy in the metastatic setting has shown substantial efficacy, with objective RRs ranging from 30% to 58% [7,9,10,12,20].

Although few reports have assessed the efficacy and safety of the combination of docetaxel and gemcitabine as NAC [13,14], an overall RR of 71.4% (95% CI, 53.7–85.4), with eight complete and 17 partial responses, was found in a previous neoadjuvant study that enrolled 35 patients with stage II–III breast cancer [13]. Furthermore, breast conservation was possible in 59% of the patients.

Here, we conducted a multicenter, single-arm, phase II trial to assess the efficacy and safety of combined docetaxel and gemcitabine neoadjuvant therapy. The overall clinical RRs was 65.3%. Furthermore, the combination therapy was advantageous for large or locally advanced breast cancer with respect to breast conservation (76.5%). These results are consistent with the results of a previous neoadjuvant study on patients with stage II–III breast cancer [13,16].

In terms of overall clinical RRs, the present study did not show a significant superiority in pCR over previous neoadjuvant studies using docetaxel. The different characteristics and different cycles and sequences of drug administration of the patients might have contributed to the relatively low rate of pCR in the current study. First, our cohort included four subtypes with different HR and HER2 status. In general, patients with HER2-positive and triple-negative breast cancer (TNBC) have high RRs, while those with HR-positive breast cancer have low RRs to NAC [21]. However, the sample size of each subtype in this study is inadequate to draw a generalized conclusion on the efficacy of the combination of docetaxel and gemcitabine as a NAC regimen. Further NAC trials should be designed to assess HR-positive, HER2-positive, and TNBC cohorts separately in a large population. Second, this result might have also been influenced by the dose reduction of the current NAC regimen that was necessitated by the development of neutropenia. Although myelosuppression is generally reported as manageable and seldom leads to drug withdrawal, grade 3 and 4 neutropenia has been a major problem that caused dose reductions or delays in most previous studies of metastatic cancer that used a combination of docetaxel and gemcitabine regimen [7,9,10,12,20]. In the current study, hematological toxicity, particularly neutropenia, was observed in 93.9% of the patients. Dose reductions were required in 32.6% of these patients. The rates of neutropenia and dose reduction were significantly higher than those reported in previous studies of metastatic disease [20]. A previous neoadjuvant study using docetaxel and gemcitabine achieved low rates of neutropenia and febrile neutropenia using pegfilgrastim as primary prophylaxis [22]. Pegfilgrastim has been shown to be superior to filgrastim in preventing severe neutropenia, which may result in a better dosing schedule [23]. Third, the above result might also have been influenced by the total cycles of NAC as well as the regimen. In studies comparing the same 2-agent NAC with different numbers of treatment cycles, increasing the number of cycles generally increased the pCR and RR rates [16]. To obtain high rates of pCR, six to eight cy-

https://doi.org/10.4048/jbc.2017.20.4.340

cles of NAC has recently become the standard treatment in clinical practice [21]. Finally, although all patients with HER2-positive cancer received adjuvant trastuzumab for 1 year, these patients did not receive trastuzumab as NAC in the present study. NAC with a sequential anthracycline-taxane–based chemotherapy in combination with trastuzumab is currently the preferred therapy for patients with HER2-positive breast cancer and is based on the high pCR rate with the addition of trastuzumab compared with chemotherapy alone [24]. The use of the combination of docetaxel and gemcitabine as NAC regimen with trastuzumab might have contributed to the improvement of pCR in the current study. However, a trial level of correlation between the rate of pCR improvement and its effect on outcome has not yet been found [25].

The above findings raised concerns that the efficacy may have been compromised due to insufficient exposure to chemotherapy regimens. Despite potential insufficient exposure to chemotherapy regimens due to the high rate of dose reduction and the use of short cycles of NAC, the rate of breast-conserving surgery and the overall clinical RRs were comparable with those of previous studies. Therefore, we expect that overcoming these limitations through sufficient exposure to chemotherapy regimens may result in better efficacy, including RR and pCR.

In conclusion, the current single-arm phase II trial did not show that the combination of docetaxel and gemcitabine significantly improves pCR. However, as NAC with docetaxel and gemcitabine was effective in terms of the rate of breast-conserving surgery as well as the overall clinical RRs, this regimen has potential as a therapeutic option. Based on our results, we recommend that further prospective neoadjuvant trials with primary prophylaxis using G-CSF, extended cycles, and larger numbers of patients with stage II–III breast cancer should be conducted to determine the best therapeutic strategy for achieving optimum efficacy of the combination of docetaxel and gemcitabine.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol 2006;24:1940-9.
2. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30:1796-804.
3. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001;19:4224-37.
4. Vriens BE, Aarts MJ, de Vries B, van Gastel SM, Wals J, Smilde TJ, et al. Doxorubicin/cyclophosphamide with concurrent versus sequential docetaxel as neoadjuvant treatment in patients with breast cancer. Eur J Cancer 2013;49:3102-10.
5. Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol 1999;17:460-9.
6. Mavroudis D, Malamos N, Alexopoulos A, Kourousis C, Agelaki S, Sarra E, et al. Salvage chemotherapy in anthracycline-pretreated metastatic breast cancer patients with docetaxel and gemcitabine: a multicenter phase II trial. Ann Oncol 1999;10:211-5.
7. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, 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;20:2812-23.
8. Kelly CM, Green MC, Broglio K, Thomas ES, Brewster AM, Valero V, et al. Phase III trial evaluating weekly paclitaxel versus docetaxel in combination with capecitabine in operable breast cancer. J Clin Oncol 2012;30:930-5.
9. Del Mastro L, Fabi A, Mansutti M, De Laurentiis M, Durando A, Colantuoni G, et al. Phase III trial of first-line treatment with gemcitabine plus docetaxel versus gemcitabine plus paclitaxel in women with metastatic breast cancer (MBC): a comparison of different schedules and treatment. 2012 ASCO Annual Meeting. 2012;30. Abstract #1073.
10. Tomova A, Bartsch R, Brodowicz T, Tzekova V, Timcheva C, Wiltschke C, et al. Concomitant docetaxel plus gemcitabine versus sequential docetaxel followed by gemcitabine in anthracycline-pretreated metastatic or locally recurrent inoperable breast cancer patients: a prospective multicentre trial of the Central European Cooperative Oncology Group (CECOG). Breast Cancer Res Treat 2010;119:169-76.
11. Heinemann V. Role of gemcitabine in the treatment of advanced and metastatic breast cancer. Oncology 2003;64:191-206.
12. Joensuu H, Sailas L, Alanko T, Sunela K, Huuhtanen R, Utriainen M, et al. Docetaxel versus docetaxel alternating with gemcitabine as treatments of advanced breast cancer: final analysis of a randomised trial. Ann Oncol 2010;21:968-73.
13. Estévez LG, Sánchez-Rovira P, Dómine M, León A, Calvo I, Jaén A, et al. Biweekly docetaxel and gemcitabine as neoadjuvant chemotherapy followed by adjuvant doxorubicin and cyclophosphamide therapy in stage II and III breast cancer patients: results of a phase II study. Clin Transl Oncol 2007;9:317-22.
14. Yardley DA. Gemcitabine and docetaxel in metastatic and neoadjuvant treatment of breast cancer. Semin Oncol 2004;31(2 Suppl 5):37-44.
15. Diéras V, Fumoleau P, Romieu G, Tubiana-Hulin M, Namer M, Mauriac L, et al. Randomized parallel study of doxorubicin plus paclitaxel and doxorubicin plus cyclophosphamide as neoadjuvant treatment of pa-

tients with breast cancer. J Clin Oncol 2004;22:4958-65.
16. Buzdar AU. Preoperative chemotherapy treatment of breast cancer: a review. Cancer 2007;110:2394-407.
17. Smorenburg CH, Bontenbal M, Seynaeve C, van Zuylen C, de Heus G, Verweij J, et al. Phase II study of weekly gemcitabine in patients with metastatic breast cancer relapsing or failing both an anthracycline and a taxane. Breast Cancer Res Treat 2001;66:83-7.
18. Rha SY, Moon YH, Jeung HC, Kim YT, Sohn JH, Yang WI, et al. Gemcitabine monotherapy as salvage chemotherapy in heavily pretreated metastatic breast cancer. Breast Cancer Res Treat 2005;90:215-21.
19. Modi S, Currie VE, Seidman AD, Bach AM, Panageas KS, Theodoulou M, et al. A phase II trial of gemcitabine in patients with metastatic breast cancer previously treated with an anthracycline and taxane. Clin Breast Cancer 2005;6:55-60.
20. Metro G, Fabi A, Russillo M, Papaldo P, De Laurentiis M, Ferretti G, et al. Taxanes and gemcitabine doublets in the management of HER-2 negative metastatic breast cancer: towards optimization of association and schedule. Anticancer Res 2008;28:1245-58.
21. Yang Y, Im SA, Keam B, Lee KH, Kim TY, Suh KJ, et al. Prognostic impact of AJCC response criteria for neoadjuvant chemotherapy in stage II/III breast cancer patients: breast cancer subtype analyses. BMC Cancer 2016;16:515.
22. McCarthy N, Boyle F, Zdenkowski N, Bull J, Leong E, Simpson A, et al. Neoadjuvant chemotherapy with sequential anthracycline-docetaxel with gemcitabine for large operable or locally advanced breast cancer: ANZ 0502 (NeoGem). Breast 2014;23:142-51.
23. von Minckwitz G, Kümmel S, du Bois A, Eiermann W, Eidtmann H, Gerber B, et al. Pegfilgrastim +/- ciprofloxacin for primary prophylaxis with TAC (docetaxel/doxorubicin/cyclophosphamide) chemotherapy for breast cancer: results from the GEPARTRIO study. Ann Oncol 2008;19:292-8.
24. Von Minckwitz G, Loibl S, Untch M. What is the current standard of care for anti-HER2 neoadjuvant therapy in breast cancer? Oncology (Williston Park) 2012;26:20-6.
25. Wuerstlein R, Harbeck N. Neoadjuvant therapy for HER2-positive breast cancer. Rev Recent Clin Trials 2017;12:81-92.

 https://doi.org/10.4048/jbc.2017.20.4.340