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ORIGINAL ARTICLE

Efficacy and toxicity of preoperative chemotherapy with docetaxel and epirubicin in locally advanced invasive breast cancer

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Summary

Purpose: *To investigate the efficacy and safety of neoadjuvant chemotherapy with docetaxel plus epirubicin with granulocyte colony-stimulating factor (G-CSF) support in locally advanced breast cancer patients.*

Methods: *We retrospectively evaluated the records of 39 patients with locally advanced breast cancer. All of them received neoadjuvant epirubicin 75 mg/m^2 plus docetaxel 75 mg/m^2 every 3 weeks with G-CSF support. Responding patients were subjected to breast-conserving or modified radical mastectomy.*

Results: *Four (10.3%) patients achieved clinical complete response (cCR) and 25 (64.1%) clinical partial response (cPR). Pathologic complete response (pCR) was observed in 4 patients with cCR. Ten (25.6%) patients achieved stable disease (SD), while no patient had progressive disease (PD). Grade 3 and 4 neutropenia was observed in 6 (15.3%) and 4 cases (10.3%), respectively. Febrile neutropenia was observed in 2 (5.1%) cases and anemia in 7 (17.9%) cases. Grade 1/2 mucositis was observed in 12 (30.7%) patients and grade 1/2 peripheral neuropathy in 7 (17.9%) patients. Dose reduction was necessary in 4 patients with grade 4 neutropenia. The median disease-free survival was 60 months (95% CI: 41-79 months). Median overall survival was not reached. Five-year overall survival was 64.2%.*

Conclusion: *The combination of docetaxel plus epirubicin was active and tolerable in neoadjuvant treatment of locally advanced breast cancer.*

Key words: docetaxel, efficacy, epirubicin, locally advanced breast cancer, neoadjuvant chemotherapy, toxicity

Introduction

Preoperative systemic chemotherapy is a standard treatment approach for locally advanced breast cancer and offers a higher probability for breast-conserving surgery for selected patients with locally advanced breast cancer [1-4]. The goals of a preoperative chemotherapeutic approach in locally advanced breast cancer are to reduce the size of the primary tumor, rendering breast-conserving operation possible, and to improve overall survival by eradicating micrometastatic disease [5,6]. Furthermore, pCR which is associated with longer disease-free and overall survival is also one of the primary goals [7]. Most trials of with anthracycline-containing regimens for preoperative chemotherapy showed clinical and pathological response rates in the range of 61-83.5% and 9.6-15%, respectively. pCR has been reported between 15-36% with taxane regimens [1,8-13]. Furthermore, the addition of trastuzumab in HER-2 positive cases in preoperative taxane regimens has been reported to achieve pCR in as many as 39-75% of the patients [12,14-17].

The aim of this study was to retrospectively evaluate the efficacy and safety of neoadjuvant chemotherapy with docetaxel and epirubicin plus G-CSF support in locally advanced breast cancer.

Methods

Patients

The medical records of 39 patients with locally advanced breast cancer (stage IIB, IIIA, IIIB and IIIC, according to AJCC TNM system) treated between July 1999 to January 2009 with neoadjuvant docetaxel plus

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epirubicin combination chemotherapy were retrospectively evaluated. Histological confirmation of invasive breast cancer was performed by core needle biopsy. Patient performance status was estimated by ECOG criteria. Disease staging was performed at baseline with clinical examination, mammography, breast and liver ultrasonography, chest x-ray and bone scan. PET CT was used in selected patients.

Patients had adequate bone marrow function (white blood cell count $>3\times10^9$/l, platelets $>100\times10^9$/l, hemoglobin >10 g/dl), liver function (total bilirubin <2 mg/dl, aspartate aminotransferase or alanine aminotransferase < 3× upper limit of normal) and renal function (blood urea nitrogen < 30 mg/dl, creatinine <1.5× upper limit of normal). Cardiac function was assessed with electrocardiography, telecardiography and in many patients with echocardiography.

Treatment

Patients received epirubicin 75 mg/m^2 (30 min i.v. infusion) followed by docetaxel 75 mg/m^2 infused over 1 h. G-CSF was used for prophylaxis of febrile neutropenia in all patients (5 μg/kg/day s.c. on days 3-5). All patients were evaluated after 2 cycles of chemotherapy. Responding patients (CR+PR) received 2 or more additional cycles of the combination, whereas those with SD received a different regimen or underwent surgery. During the study period, HER2/new positive patients did not receive trastuzumab because this agent had not been approved for neoadjuvant therapy in our country at that time. All patients received 32 mg/day methylprednisolone before the day, on the day and after the day of treatment to prevent docetaxel hypersensitivity for all chemotherapy cycles. 5-HT3 antagonists and 8 mg dexamethasone were given before each chemotherapy cycle for emesis prevention for one day.

Patients thought to have a maximal response underwent breast-conserving or modified radical mastectomy with axillary lymph node dissection within 4 weeks after the last chemotherapy cycle. Postoperatively, those patients received adjuvant chemotherapy with the same regimen. All patients received radiation therapy to the chest wall and regional lymph node areas after adjuvant chemotherapy. Endocrine treatment started in patients with estrogen (ER) and/or progesterone receptor (PR) positive tumors after adjuvant chemotherapy and radiation.

Response and toxicity evaluation

Response assessment to chemotherapy was performed every 2 cycles with physical examination, breast and liver ultrasonography and chest x-ray according to the RECIST criteria. Responses were defined as cCR (disappearance of all assessable disease), cPR (reduction of more than 30% in the two largest tumor diameters), cSD (neither PR nor PD) and cPD (increase of more than 25% in tumor size or appearance of new lesions). A pCR was defined as no residual tumor in the breast and lymph nodes or residual *in situ* carcinoma.

Complete serum biochemistry and full blood count were performed at baseline, before and at the end of each cycle. Full blood counts were also repeated on days 7 and 10 of each cycle to estimate blood cells nadir.

Statistical analysis

Based on the intention-to-treat principle, data of all enrolled patients were used in statistical analysis. Overall survival was defined as the period from the diagnosis until death from any cause or until the date of the last follow-up. Disease-free survival was defined as the period from the day of surgery until local/distant/contralateral breast disease relapse. Both overall and disease-free survival were estimated by the Kaplan-Meier method. SPSS 12 programme was used for statistical analysis. Survival curves were compared with the log-rank test. P-values less than 0.05 were accepted as significant.

Results

Patient characteristics

Patient characteristics are shown in Table 1. The median age was 50 years (range 30-79). Thirteen (33.2%) patients were pre- or perimenopausal and 26 (66.8%) were postmenopausal. ECOG performance status was between 0-2. The histology of all patients was invasive ductal cancer. Both ER and PR status was positive in 20 (51.3%) patients and unknown in 5 (12.8%). Sixteen (41%) patients had positive HER2/neu by IHC 3+ or FISH. The median largest tumor size was 37 mm (range 15-80).

Overall, 140 cycles of treatment were administered in all patients. Eighteen received 3 cycles of neoadjuvant chemotherapy, 26 received 4 cycles and one received one cycle. Responding patients (CR+PR) underwent breast-conserving surgery or modified radical mastectomy. Patients with SD also underwent modified radical mastectomy. During neoadjuvant chemotherapy, cardiac toxicity or allergic side effects did not occur.

Response to preoperative chemotherapy

Responses to neoadjuvant chemotherapy are summarized in Table 2. Four (10.3%) patients achieved cCR

Table 1. Pretreatment characteristics of 39 patients

Characteristics	*n (%)*
Age	
median	50
range	30-79
ECOG performance status	
0-1	36 (92.4)
2	3 (7.6)
Menopausal status	
premenopausal	13 (33.2)
postmenopausal	26 (66.8)
Biopsy-proven histology	
invasive ductal carcinoma	33 (100)
invasive lobular carcinoma	0
Tumor grade	
1-2	12 (30.7)
3	27 (69.3)
Estrogen receptor status	
positive	20 (51.3)
negative	14 (35.9)
unknown	5 (12.8)
Progesterone receptor status	
positive	20 (51.3)
negative	14 (35.9)
unknown	5 (12.8)
HER2/neu status	
positive (FISH + or IHC 3+)	16 (41)
negative	19 (48.7)
unknown	4 (10.3)
Stage of disease	
IIB	6 (15.3)
IIIA	17 (43.8)
IIIB	9 (23)
IIIC	7 (17.9)
Tumor size	
T1	2 (5.1)
T2	14 (35.9)
T3	12 (30.7)
T4	11 (28.3)
Lymph node status	
N0	2 (5.1)
N1	13 (33.2)
N2	17 (43.8)
N3	7 (17.9)

and 25 (64.1%) cPR, for an objective response rate of 74.4%. The 4 cCR patients had also pCR. Of 29 CR and PR patients 12 (41.3%) underwent breast-conserving surgery and 17 (58.7%) modified radical mastectomy. Ten (25.6%) patients showed SD and were subjected to modified radical mastectomy, while no patient developed PD during neoadjuvant therapy. Table 3 displays responses according to disease stage on presentation.

Response rates were evaluated in HER2/neu positive and negative subgroups. Of 19 HER2/neu negative patients, 11 (57.9%) achieved cPR and 2 (10.5%) pCR. Of 16 HER2/neu positive patients, 10 (62.5%) achieved cPR and 2 (12.5%) pCR. This difference wasn't statistically significant (p=0.608). Of 10 ER and PR negative patients, 5 (50%) achieved cPR and 2 (20%) pCR. Of 16 ER and PR positive patients, 10 (62.5%) achieved cPR and none pCR. This difference wasn't statistically significant either (p=0.292).

Treatment-related toxicity

There was no treatment-related death. Adverse events are shown in detail in Table 4. The most common hematological toxicity was neutropenia. Grade 3 and 4 neutropenia was observed in 6 (15.3%) and in 4 (10.3%) patients, respectively. Febrile neutropenia was observed in 2 (5.1%) patients with grade 4 neutropenia. No cases with thrombocytopenia were seen. Despite G-CSF support, 25% dose reduction in both drugs was necessary for the subsequent cycles in 4 patients with grade 4 neutropenia.

Table 3. Response evaluation according to initial stage of disease

Response	*Patients n (%)*	*Stage of disease*			
		IIB	*IIIA*	*IIIB*	*IIIC*
cCR	4 (10.3)	2	1	1	0
pCR	4 (10.3)				
PR	25 (64.1)	3	12	6	4
SD	10 (25.6)	1	4	2	3

cCR: clinical complete response, pCR: pathological complete response, PR: partial response, SD: stable disease

Table 2. Response rates according to ER and HER2/neu status

Response	*Patients, n (%)*	*Patients, n*			*Patients, n*		
		HER2+	*HER2–*	*unknown*	*ER+*	*ER–*	*unknown*
Clinical response							
Complete response	4 (10.3)	2	2	0	1	3	0
Partial response	25 (64.1)	10	11	4	11	11	3
Stable disease	10 (25.6)	4	6	0	7	3	0
Progressive disease	0	0	0	0	0	0	0
Pathological response							
Complete response	4 (10.3)	2	2	0	1	3	0

Table 4. Treatment-related toxicities

	Patients n (%)	*Grade 1-2 n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Nausea-vomiting	16 (41)	16 (41)	0	0
Neutropenia	20 (51.3)	10 (25.7)	6 (15.3)	4 (10.3)*
Anemia	7 (17.9)	7 (17.9)	0	0
Thrombocytopenia	0	0	0	0
Mucositis	12 (30.7)	12 (30.7)	0	0
Diarrhea	5 (12.8)	5 (12.8)	0	0
Peripheral neuropathy	7 (17.9)	7 (17.9)	0	0

*2 patients had neutropenic fever

Survival

The median follow-up was 76 months (range 7-107). During follow-up, 5 of 39 patients relapsed after surgery and died of progressive disease. Thirty-four patients are alive and under follow-up. The median disease-free survival for all patients was 60 months (95% CI: 41-79 months; Figure 1). The median overall survival hasn't been reached. Five-year overall survival was 64.2% (Figure 2).

In objective responders (CR+PR) and in SD patients, the median disease-free survival was 66 months (95% CI: 42-90) and 44 months (95% CI: 32-48), respectively (p=0.228; Figure 3). In addition, in objective responders (CR+PR) and those with SD, the 5-year overall survival has not been reached (67.52% and 66.67%, respectively; p=0.797; Figure 4).

Discussion

We evaluated the efficacy and safety of neoadjuvant chemotherapy with docetaxel and epirubicin plus G-CSF support in locally advanced breast cancer. The treatment was effective and well-tolerated. The median disease-free survival was 60 months. Four (10.3%) patients achieved pCR and 25 (64.1%) cPR. No PDs were seen and all patients underwent breast-conserving surgery or modified radical mastectomy after neoadjuvant therapy. The most common adverse effects were neutropenia (51.3%), nausea-vomiting (41%), mucositis (30.7%), peripheral neuropathy (17.9%) and anemia (17.9%). Two of patients with grade 4 neutropenia developed neutropenic fever.

Neoadjuvant chemotherapy offers several advantages in locally advanced breast cancer. It increases the possibility of breast-conserving surgery by downstaging the primary tumor. Furthermore, neoadjuvant chemotherapy allows testing the chemosensitivity of the primary tumor and may be effective in obtaining control of micrometastases [13,18]. Preoperative chemotherapy does not offer survival advantage when compared with adjuvant chemotherapy. However, some investigators have reported that the achievement of a pCR improve the relapse-free survival [19-21].

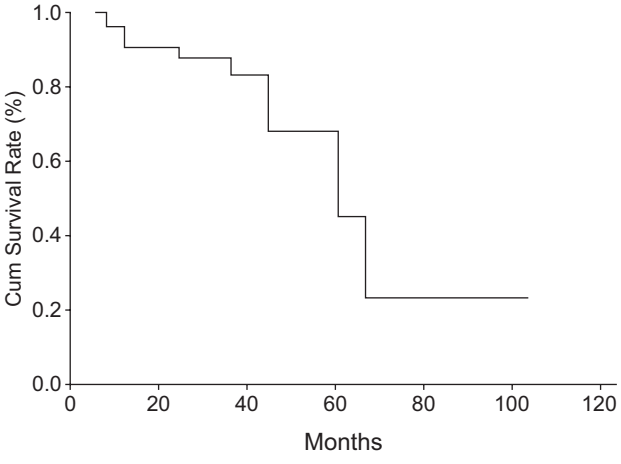

Figure 1. Disease-free survival. The median disease-free survival was 60 months (95% CI: 41-79).

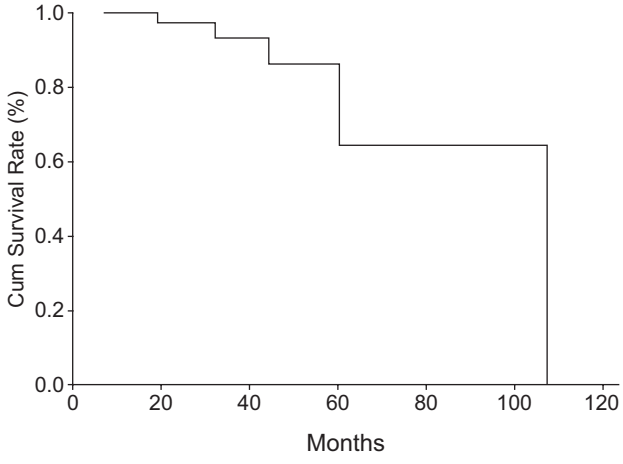

Figure 2. Overall survival. Median overall survival hasn't been reached. Five-year overall survival was 64.2%.

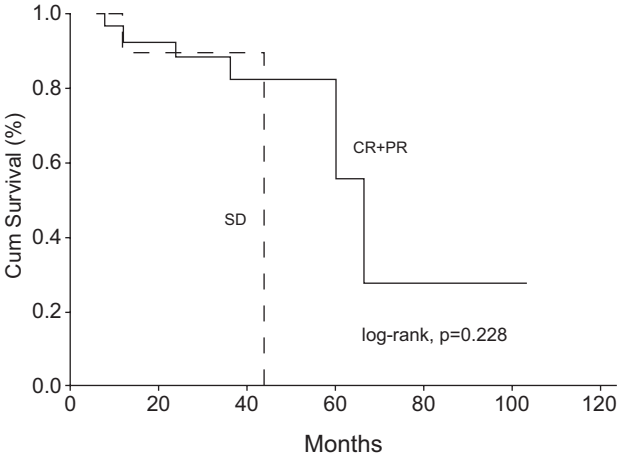

Figure 3. In objective responders (CR+PR) and those with SD, median disease-free survival was 66 months (95% CI: 42-90) and 44 months (95% CI: 32-48), respectively (log rank, p=0.228).

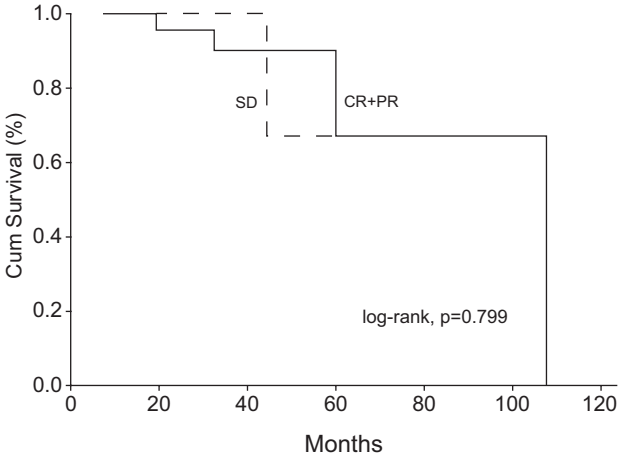

Figure 4. In both objective responders (CR+PR) and those with SD, 5-year overall survival has not been reached (67.52% and 66.67% respectively; log rank, p=0.797).

pCRs achieved with neoadjuvant chemotherapy were associated with better outcome regardless of hormone receptors status in breast cancer patients [22]. However, the optimal dose and combination of cytotoxic agents as well as the number of treatment cycles is still a matter of investigation.

In two phase II studies the reported objective response rate ranged between 76.7 and 83.3%, and the pCR rate reached 13.3% with the addition of a taxane to anthracycline-based regimens [7,23]. In the study by Matteis et al. with neoadjuvant docetaxel plus epirubicin, the most common adverse reactions were 80% grade 4 neutropenia, 33.3% neutropenic fever, 63.3% anemia, 50% nausea and 43.3% mucositis [23]. In contrast, in our study, both hematological and non-hematological toxicities were lower and tolerable than in that study. In another phase II trial, Ramaswamy et al. reported a high pCR rate (28%) in patients who received 3 cycles of docetaxel (100 mg/m^2 every 3 weeks), followed by 3 cycles of epirubicin (100 mg/m^2 every 3 weeks) in stage II/III breast cancer patients [24]. In some studies, the clinical response and pCR rates were up to 95% and 34%, respectively, with the addition of taxanes to a preoperative chemotherapy containing anthracycline in locally advanced breast cancer [25-29]. In our study, the clinical response and pCR rates were 74.4% and 10.3%, respectively.

The most effective timing and sequencing for induction chemotherapy are not completely clear. Several approaches are under consideration such as variations in dose, dose density, combination and sequencing of chemotherapeutic agents, number of treatment cycles or initial treatment of patients with small breast cancers primarily suitable for surgery [11,15,17,30,31].

In two important phase III studies, 6 cycles of epirubicin and docetaxel were compared with 3 cycles as neoadjuvant treatment in patients with stage II and III breast cancer. In both studies, the pCR rates of the primary tumor were higher in patients receiving 6 cycles than in those receiving 3 cycles. In addition, in both studies the treatment-related toxicities were tolerable [11,32]. The ABCSG-14 trial enrolled 292 breast cancer patients who received neoadjuvant chemotherapy with docetaxel plus epirubicin with G-CSF support and were assigned to receive 6 or 3 cycles. In the 6 cycles arm a higher pCR rate (18.6 vs. 7.7%; p=0.0045) and a higher negative axillary node rate (56.6 vs. 42.8; p=0.02) were registered, compared with the 3 cycles arm. In both arms, the rates of adverse events were similar, the most common being hematological (22 cases, 7.6%), infection (12 cases, 4.2%) and gastrointestinal (6 cases, 2.1%) [32].

Hormone receptor negativity predicts higher probability for achieving a pCR after neoadjuvant chemotherapy. While this effect is only reported in patients with negative ER, no adequate data exist with the PR status [30-33]. In two recent studies that included taxane and/or anthracycline, pCR rates were 29% and 67% in ER negative and HER2/neu positive breast cancer patients [22,30]. Although ER negativity is clearly important for predicting sensitivity to cytotoxic chemotherapy, PR may be more important for predicting sensitivity to hormonal treatment [32]. Moreover, the pCR rates were higher in patients with hormone receptor negative and HER2/neu positive breast cancer who were treated with trastuzumab-containing regimens in a neoadjuvant setting [12,15-17]. In our study, of 4 patients with pCR, 3 (75%) were hormone receptor negative and HER2/

neu positive and one (25%) patient was ER and PR positive and HER2/neu negative.

The rates of pCR are significantly higher (60-75%) in patients with HER2/neu positive disease with trastuzumab and taxanes-containing regimens [15-17]. In our study, however, pCR was only 12.5% with the combination of docetaxel and epirubicin. As stated previously, we could not use trastuzumab in these patients because its administration was not approved for neoadjuvant therapy during the study period. However, nowadays there is no doubt for using trastuzumab in these patients in neoadjuvant treatments, including our country.

In conclusion, the combination of docetaxel plus epirubicin was found to be active and tolerable as neoadjuvant treatment of locally advanced breast cancer. However, patients who have HER2/neu positive disease should be treated with a combination including trastuzumab. pCR rate may be increased by strategies such as prolongation of treatment, sequential combinations of treatment with trastuzumab for HER2/neu positive breast cancer patients, or with new combinations.

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