Pathological complete response rates comparing 3 versus 6 cycles of epidoxorubicin and docetaxel in the neoadjuvant setting of patients with stage II and III breast cancer

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We conducted a prospective randomized study to compare the results of 3 cycles of epidoxorubicin/docetaxel to 6 cycles of epidoxorubicin/docetaxel prior to surgery in breast cancer patients with clinical stages II and III. Forty-five patients eligible for neoadjuvant chemotherapy were randomly assigned to receive either 3 (group 1) or 6 (group 2) cycles of epidoxorubicin/docetaxel prior to surgery. Chemotherapy consisted of epidoxorubicin 75 mg/m^2 and docetaxel 75 mg/m^2 on day 1 in 3-week cycles. The primary endpoint was the pathological complete response (pCR) rate; secondary endpoints were the rates of breast-conserving surgery and the axillary lymph node status in both groups. A pCR occurred in 10% (two of 20) in Group 1 and in 36% (nine of 25) in Group 2, which was statistically significant ($p=0.045$). Breast-conserving surgery could be performed in 70% (14 of 20) in Group 1 and in 76% (19 of 25) in Group 2 ($p=0.065$). Axillary lymph node status was negative in 45% (nine of 20) in Group 1 and 52% (13 of 25) in Group 2 ($p=0.86$). We conclude that 6 cycles of pre-operative epidoxorubicin/docetaxel versus 3 cycles of pre-operative epidoxorubicin/docetaxel significantly increases the pCR rates for breast cancer patients. *Anti-Cancer Drugs* **16:867–870 © 2005 Lippincott Williams & Wilkins.**

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Introduction

Neoadjuvant chemotherapy is an accepted standard of care for patients with locally advanced breast cancer. One of the first reports on neoadjuvant chemotherapy derives from Fisher *et al.* [1]. After the development of this concept in the animal model, the NSABP B-18 trial, initiated in 1988, was the first randomized trial that evaluated the effect of pre-operative systemic therapy compared with adjuvant systemic therapy after surgery. The results of this trial showed that 4 cycles of doxorubicin and cyclophosphamide given pre-operatively had no statistically significant difference in overall survival and disease-free survival compared with 4 cycles of the same regimen given post-operatively. However, patients in the pre-operative treatment arm had higher rates of breast-conserving surgical procedures compared with the adjuvant treatment arm. Hence, the reduction of tumor size and therefore reduction of mastectomy rates was the first aim of neoadjuvant chemotherapy [2–6]. Another advantage of neoadjuvant chemotherapy is the direct visualization of tumor response to therapy, which can never be observed in the adjuvant setting. A third advantage is the start of systemic therapy and the treatment of micrometastases at the earliest possible date. The initial reports on neoadjuvant chemotherapy derived from patients with advanced breast cancer, and clinical partial response rates ranged from 80 to 90% and clinical complete response rates ranged from 5 to 13% [6,7]. Nevertheless neoadjuvant chemotherapy could improve overall survival and disease-free survival in a certain subgroup of patients. There are a number of papers that report on an improved disease-free survival rate in patients with a pathological complete response (pCR) to neoadjuvant chemotherapy. Newer reports showed that tumor size prior to chemotherapy, duration and density of chemotherapy or combination with other agents such as taxanes could improve pCR rates significantly by 3–15% [9–12]. The consequence of these findings suggests improved pCR rates. This can be achieved by inclusion of patients with tumors suitable for primary surgery and by optimization of neoadjuvant therapy protocols. We conducted this study to compare 3 cycles of epidoxorubicin and docetaxel with 6 cycles of epidoxorubicin and docetaxel in the neoadjuvant setting.

Patients and methods

Forty five patients were randomly assigned to receive 3 cycles of epidoxorubicin 75 mg/m^2 i.v. and docetaxel 75 mg/m^2 i.v. on day 1 every 3 weeks or to receive 6 cycles of the same regimen. Granulocyte colony-stimulating

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factor was administered on days 3–10 if necessary. Included were patients with primary invasive breast cancer of stage II and III scheduled to receive neoadjuvant chemotherapy. Preoperative assessment of tumor size was performed by ultrasound and mammography. Histological type, grading, hormone receptor status and HER-2/*neu* status were evaluated by core needle biopsy prior to therapy. All patients were negative for distant metastases (negative chest X-ray, negative ultrasound of the abdomen and negative bone scan). None of the patients had a contraindication to receive epidoxorubicin and docetaxel chemotherapy. All patients gave informed consent and the study was approved by the local ethics committee. Primary study endpoint was to compare the rates of pCR; secondary study endpoints were to compare the rates of breast-conserving surgical procedures and to compare the axillary lymph node involvement after neoadjuvant therapy in both treatment arms. A pathological response was defined as complete (pCR) when no invasive tumor, or *in situ* carcinoma only, could be detected by the histopathologic examination of the excised breast tissue.

Twenty patients were assigned to Group 1 (3 cycles) and 25 patients were assigned to Group 2 (6 cycles). Patients in both groups were comparable according to age ($p = 0.65$), tumor size prior to induction therapy ($p = 0.53$), histology ($p = 0.37$), grading ($p = 0.51$), hormone receptor status ($p = 0.59$) and HER-2/*neu* status ($p = 0.59$) (Table 1). All patients completed the proposed treatment regimen.

Statistical analysis

Independent Student's *t*-tests and tests for the difference of two independent proportions were used to compare the variables age, tumor size prior to chemotherapy, histology, grading, hormone receptor status, HER-2/*neu* status, axillary lymph node status and surgical procedure. The proportion of pCR in both groups was compared with Barnard's unconditional test of superiority. The corresponding hypotheses were two-sided. Additional tests and exact 95% confidence intervals (CIs) for the difference and for the ratio of two binominal proportions with corresponding *p* values were computed based on the Monte-Carlo method. A *p* value less than 5% was considered as statistically significant different. This study achieves a power of approximately 80% to detect a difference of 35% or more between Group 1 and Group 2. For this power analysis, a pCR rate of 10% is assumed in Group 1. All computations were done with Statistica (StatSoft, Tulsa, Oklahoma, USA) and StatXact 5 (Cytel Software, Cambridge, Massachusetts, USA).

Results

All 45 patients completed the proposed treatment. Two patients ($P_1 = 10\%$) had a pCR in Group 1 (95% CI 1–32%) and nine patients ($P_2 = 36\%$) had a pCR in Group 2 (95% CI 18–58%), $p = 0.045$ (Table 1). The

Table 1 **Patient characteristics**

	Epidoxorubicin/docetaxel × 3	Epidoxorubicin/docetaxel × 6	*p*
Age (years)			
min	33	28	
max	62	62	
mean	47.1	45.7	0.65
Tumor size prior to chemotherapy (mm)			
min	20	20	
max	70	65	
mean	36.5	34.1	0.53
Histology [*n* (%)]			0.37
invasive ductal carcinoma	18 (90)	20 (80)	
invasive lobular carcinoma	2 (10)	5 (20)	
Grading [*n* (%)]			0.51
grade 2	9 (45)	8 (32)	
grade 3	11 (55)	17 (68)	
Hormone receptor status [*n* (%)]			0.59
ER^+/PR^+	6 (30)	9 (36)	
ER^+/PR^-	1 (5)	3 (12)	
ER^-/PR^-	13 (65)	13 (52)	
ER^-/PR^+			
HER-2/*neu* status [*n* (%)]			0.59
HER-2/neu^+	3 (15)	5 (20)	
HER-2/neu^-	17 (85)	20 (80)	
Axillary lymph node status [*n* (%)]			0.86
negative	9 (45)	13 (52)	
positive	11 (55)	12 (48)	
Response to chemotherapy [*n* (%)]			
clinical partial/complete response	18 (90)	16 (64)	
pCR	2 (10)	9 (36)	0.045
Surgery [*n* (%)]			0.65
mastectomy	6 (30)	6 (24)	
wide excision	14 (70)	19 (76)	

Table 2 Tumor characteristics of patients with pCR

Pre-operative chemotherapy	Age (years)	Pre-chemotherapy					Post-chemotherapy			
		Primary tumor size (mm)	Histology	Grading	ER/PR	HER-2/neu	Surgery	ypT status	ypN status	Positive nodes/total nodes
ET × 3	60	27	IDC	2	−/−	0	WE	ypT0	ypN2a	4/8
ET × 3	34	35	IDC	3	−/−	0	WE	ypT0	yN0	0/22
ET × 6	54	30	IDC	2	−/−	3	WE	ypTis	yN1mi(sn)	1/25
ET × 6	50	35	IDC	3	−/−	3	ME	ypT0	yN0	0/17
ET × 6	31	35	IDC	2	+/+	2	WE	ypT0	yN0	0/13
ET × 6	60	60	ILC	3	−/−	0	ME	ypT0	yN0	0/10
ET × 6	62	20	IDC	3	+/+	0	WE	ypT0	yN1mi(sn)	1/41
ET × 6	49	40	IDC	3	+/−	3	WE	ypT0	yN0	0/13
ET × 6	62	30	IDC	3	+/−	2	WE	ypT0	yN0	0/19
ET × 6	49	35	IDC	3	−/−	3	WE	ypTis	yN0	0/16
ET × 6	46	26	IDC	3	−/−	0	WE	ypT0	yN0	0/18

IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, ER = estrogen receptor, PR = progesterone receptor, WE = wide excision, ME = mastectomy.

exact 95% CI for the difference of P_2–P_1 ranges from 0.7 to 49.8%. The p value of the corresponding test is $p = 0.045$. The exact 95% CI for the ratio of P_1–P_2 ranges from 0.03 to 0.99 ($p = 0.049$). Two of the nine patients in Group 2 had small areas of ductal carcinoma *in situ* in the pathologic specimen, but presented with 30- and 35-mm invasive carcinomas prior to chemotherapy (Table 2). There was no statistically significant difference in axillary lymph node status after chemotherapy in both groups, $p = 0.86$. Axillary lymph node status after induction chemotherapy was positive in 11 patients (55%) in Group 1 and in 12 patients (48%) in Group 2, respectively, and negative in nine patients (45%) in Group 1 and in 13 patients (52%) in Group 2, respectively. There was no statistically significant difference according to the surgical procedure, $p = 0.65$. Six patients (30%) in Group 1 and six patients (24%) in Group 2, respectively, had a mastectomy. Breast-conserving surgery could be performed in 14 patients (70%) in Group 1 and in 19 patients (76%) in Group 2.

One patient in Group 1 who had pCR in the breast revealed four positive lymph nodes in the axilla, developed cerebral metastases 9 months after surgery and died 2 months later. The second patient with pCR in Group 1 had negative axillary lymph nodes.

Each of two patients in Group 2 who had pCR in the breast had one micrometastasis in one lymph node in the axilla, which was the sentinel lymph node. All further lymph nodes in axillary lymph node dissection were negative. The other seven patients with pCR in Group 2 had negative axillary lymph nodes.

Discussion

Primary systemic therapy was adopted to treat patients with locally advanced breast cancers who were not suitable for primary surgery. In the next step primary chemotherapy was used to treat patients who were not suitable for breast-conserving surgery due to their tumor size. Substantial numbers of patients respond well with a significant reduction in tumor sizes and therefore are candidates for breast-conserving surgery. Primary chemotherapy is increasingly used in patients with smaller breast cancers, who are suitable for surgery as initial treatment. In many studies clinical partial and complete response rates of 75–90% were obtained. However, pCR rates were very low. The efficacy of neoadjuvant chemotherapy for breast cancer depends on multiple features of the treatment regimen. Different treatment regimens are under investigation to date. The optimal dose and combination of cytotoxic substances as well as treatment intervals and number of treatment cycles have still to be evaluated, and are dependent on tumor and patient features. In more recent studies the use of newer chemotherapeutic agents, and the combination of anthracycline-based chemotherapy and taxanes with the advantage of incomplete cross-resistance different toxicity profiles, resulted in clinical response rates of up to 95% and pCR rates of 34% [9–14]. The presence of a pCR is associated with a significant increase in survival than in patients where residual tumor is still present after induction chemotherapy and thus response to induction chemotherapy may be used as a prognostic marker. The NSABP B-18 demonstrated that patients who received neoadjuvant doxorubicin/cyclophosphamide (AC) and achieved a pCR in the breast (9%) had a significantly better survival than those who did not achieve a pCR [8,15]. The question arises how to improve the pCR rate as it is presumably associated with the eradication of micrometastatic disease and may result in improved overall survival. The most effective timing and sequencing for induction chemotherapy is unclear. 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. We evaluated the influence of the number of treatment cycles of an epidoxorubicin/docetaxel containing regimen on the rate of pCR rates.

Docetaxel has been studied in sequence with doxorubicin-based neoadjuvant therapy in the NSABP B-27 trial, in the Aberdeen Breast Group trial and the GEPARDUO trial [9,16–18]. The NSABP B-27 trial enrolled 2411 women in three treatment arms and the sequential use of neoadjuvant docetaxel after AC significantly increased the pCR rate (25.6 versus 13.7%, $p < 0.001$) and reduced the rate of histologically positive lymph nodes (40.5 versus 48.5%, $p < 0.01$) compared with neoadjuvant AC alone. Von Minckwitz *et al.* [19,20] demonstrated a pCR rate of 9.7% in their studies with dose-dense doxorubicin/docetaxel (AT). The GEPARDUO trial was closed prematurely due to striking differences in the pCR rate. The sequential application of 4 cycles of AC followed by 4 cycles of docetaxel (T) was associated with an improved pCR rate in the breast (15.9%) compared with dose-dense AT (7.4%). Smith *et al.* [13] demonstrated in the Aberdeen Breast Group trial that the addition of docetaxel can improve the pCR rates (34%) after 4 cycles of an anthracycline-based multiagent neoadjuvant regime. Amat *et al.* [14] reported a high pCR rate in patients receiving 6 cycles of neoadjuvant docetaxel monotherapy (100 mg/m^2 every 21 days). The pCR rate was 19% on Chevallier's classification restricted to the breast and was 35% on Sataloff's classification. A small phase II study investigated weekly docetaxel (40 mg/m^2) in the neoadjuvant setting and observed a pCR rate of 16% [21].

The approach of our study was the comparison of 3 versus 6 cycles of neoadjuvant chemotherapy containing epidoxorubicin/docetaxel. We observed 10% pCR rate in the 3-cycle treatment arm and 36% pCR rate in the 6-cycle treatment arm, respectively. This difference was statistically significant despite the small number of patients included. We could not observe a significant difference in the rate of breast-conserving surgery. The reason for this may be the small number of patients, otherwise there was a high rate of breast-conserving surgery in both groups (70% in Group 1 and 76% in Group 2). The same is true for axillary lymph node status, where we could not observe a significant difference between the both groups. This may be due to the fact that patients with micrometastases in the sentinel lymph nodes were considered as lymph node-positive patients. How far pCR in our study will influence the disease-free survival and overall survival has to be evaluated.

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