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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

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ABSTRACT

Purpose
Dose-dense and sequential administration of cytotoxic drugs are current approaches to improve outcomes in patients with early-stage breast cancer.

Methods
This phase III study investigated 913 women with untreated operable breast cancer (T2-3, N0-2, M0) randomly assigned to receive either doxorubicin 50 mg/m^2 plus docetaxel 75 mg/m^2 every 14 days for four cycles with filgrastim support (ADOC), or doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 21 days followed by docetaxel 100 mg/m^2 every 21 days for four cycles each (AC-DOC). The primary end point was the incidence of pathologic complete (invasive and noninvasive) response (pCR) in the breast and axillary nodes. Secondary end points were predictors for pCR, clinical response, rate of breast conservation, and safety.

Results
A pCR was achieved in 94 patients (10.6%), but the likelihood was significantly greater with AC-DOC (14.3%; n = 63) than with ADOC (7.0%; n = 31) (odds ratio, 2.22; 90% CI, 1.52 to 3.24; $P < .001$). Independent predictors of attaining a pCR included the use of sequential therapy, high tumor grade, and negative hormone receptor status. The response rates detected by palpation and by imaging were significantly higher with AC-DOC (85.0% and 78.6%, respectively) than with ADOC (75.2% and 68.6%, respectively; both P values $< .001$). The rate of breast-conserving surgery was 63.4% for AC-DOC and 58.1% for ADOC ($P = .05$). Predominant grade 3/4 toxicities were leucopenia (AC-DOC, 74.2%; ADOC, 53.7%) and neutropenia (AC-DOC, 66.4%; ADOC, 44.7%) but were infrequently associated with fever (AC-DOC, 4.6%; ADOC, 3.1%).

Conclusion
Sequential AC-DOC is more effective at inducing pCR than dose-dense ADOC as preoperative treatment for patients with operable breast cancer.

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INTRODUCTION

Primary systemic (preoperative or neoadjuvant) therapy is the standard of care in patients with inoperable locally advanced or inflammatory breast cancer, and is increasingly being considered for patients with operable disease.[1,2] Comparable outcome has been found for pre- and postoperative application of various cytotoxic regimes, but in most studies lumpectomy was more often possible after preoperative treatment.[3,4] A

pathologic complete response (pCR; ie, absence of residual malignant cells at the primary tumor site) correlates strongly with improved disease-free and overall survival.[5-8]

As preoperative therapy, docetaxel used in dose-dense combination with doxorubicin (ADOC) has demonstrated meaningful efficacy (eg, in the German Preoperative Adriamycin Docetaxel [GEPARDO] trial).[9,10] Other efforts have explored the use of docetaxel in sequence with a doxorubicin (AC) -containing regimen; one pilot trial yielded higher pCR and 5-year survival rates than sequential repetition of the AC-containing regimen,[11] and one large trial (National Surgical Adjuvant Breast and Bowel Project [NSABP] B-27) showing improved pCR rates for docetaxel added after AC plus cyclophosphamide treatment.[12]

The GEPARDUO trial, reported here, compared the pathologic locoregional complete response rate achieved with preoperative administration of the 8-week dose-dense combination regimen ADOC, as studied in the GEPARDO study, with that of a 24-week sequential schedule of AC followed by docetaxel (AC-DOC), similar to one of the treatment arms in the NSABP B-27 trial. In case of equal efficacy, we would have recommended the less toxic and less expensive ADOC for further use.

PATIENTS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by local research ethics committees. All patients provided written informed consent. All data were independently verified with the source.

Study Design

Women age ≥ 18 years with unilateral, histologically proven, invasive, operable adenocarcinoma of the breast (T2-3, N0-2, M0) were enrolled. The primary tumor had to be bidimensionally measurable and at least 2 cm in the longest diameter using one of the following methods: palpation, sonography, mammography, or magnetic resonance imaging (MRI). Other eligibility criteria included Karnofsky performance status ≥ 70%; life expectancy ≥ 10 years; adequate hematologic, renal, and hepatic functions; and evidence of normal cardiac function.

Patients with the following criteria were excluded: bilateral breast cancer; any previous treatment for breast cancer including surgery, radiation, cytotoxic, or endocrine therapy; any previous malignancy other than breast cancer or noninvasive breast cancer; any previous treatment with cytotoxic drugs; pre-existing neurotoxicity more than grade 2 according to WHO criteria; active infection; and concurrent treatment with oral contraceptives or hormone replacement therapy.

Random assignment to treatment was carried out centrally in blocks of variable length. Stratification was done only for participating institutions.

Treatment Plan

Eligible patients were randomly assigned to receive either doxorubicin 50 mg/m^2 followed by docetaxel 75 mg/m^2 each on day 1 every 14 days for four cycles (ADOC), or doxorubicin 60 mg/m^2 followed by cyclophosphamide 600 mg/m^2 on day 1 every 21 days for four cycles followed by docetaxel 100 mg/m^2 every 21 days for four cycles (AC-DOC).

Both patient groups received corticosteroid and antiemetic prophylaxis as described previously.[10] Patients treated with the dose-dense ADOC regimen received prophylactic granulocyte colony-stimulating factor from days 5 to 10. In concordance to the NSABP B-27 protocol, all patients, irrespective of their hormone receptor status, received tamoxifen 20 mg orally once daily on the first day of chemotherapy until surgery. Patients with estrogen- or progesterone-positive tumors received postoperative tamoxifen treatment for 5 years, or until disease recurrence.

Chemotherapy dose reduction was not permitted. Chemotherapy was postponed for a maximum of 1 week in the event of severe toxicity. If the toxicity did not resolve in this period, no additional chemotherapy was to be administered and immediate surgery was recommended. If disease progressed during preoperative therapy, chemotherapy was to be discontinued and patients were to undergo immediate surgery.

After final clinical response assessment, patients had to be operated between 14 and 28 days after the last application of ADOC or 21 to 34 days after the last application of docetaxel, respective to the assigned treatment. Thereafter, all patients received standard radiotherapy of the remaining breast tissue or of the chest wall.

Assessments

A complete tumor assessment (comprising bilateral mammography; sonography of the breast, axilla, supraclavicular, and infraclavicular regions; breast MRI [optional]; chest x-ray; liver sonography; and bone scintigraphy) was performed within 4 weeks before random assignment to treatment. Clinical evaluation of palpable tumor and lymph nodes was repeated before each cycle and before surgery.

End Points

The primary end point, pCR, was defined as no microscopic evidence of residual viable tumor cells (invasive or noninvasive) in all resected breast specimens and axillary lymph nodes. Pathologic tumor response was graded according to Sinn et al[13]: grade 4, no microscopic evidence of residual tumor cells (invasive or noninvasive) in all resected specimens of the breast; grade 3, only residual noninvasive (in situ) tumor; grade 2, focal invasive tumor measuring ≤ 5 mm; and grade 0/1 for all remaining scenarios. If new lesions were detected, the response was graded as 0/1.

Secondary end points included clinical tumor response rates in the breast. Clinical complete response (CR) was defined as complete disappearance of all tumor signs in the breast and was assessed by both palpation and by the most appropriate imaging method. Partial response (PR) was defined as a reduction in the product of the two largest perpendicular diameters of the primary tumor size by 50% or more at the time of surgery, and was also assessed by palpation and by imaging studies. In patients with multifocal or multicentric disease, only the lesion with the largest diameter was assessed. Stable disease was defined as no significant increase or decrease in tumor size, and progressive disease was defined as the development of new, previously undetected lesions, or an increase in the size of a pre-existing lesion by ≥ 25% after at least two treatment cycles. Axillary lymph node response (NR) was not included in the assessment of clinical CR or PR. Axillary NR was defined as no evidence of enlarged axillary lymph nodes by

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palpation or sonography before surgery in patients who had enlarged axillary lymph nodes at baseline. Toxicity during chemotherapy was regarded as the worst WHO grade observed per cycle. Febrile neutropenia was defined as WHO grade ≥ 3 neutrophils concomitant with WHO grade ≥ 2 fever and no simultaneous infection (WHO grade = 0). If neutrophil data were missing, then leukocyte data were used. A breast was regarded as conserved if no autologous or heterologous reconstruction was performed

Disease-free and overall survival analyses will be reported at a later time, when follow-up data become available.

Statistical Analysis

This trial was designed to demonstrate that ADOC is not inferior to AC-DOC, with odds ratios for pCR of ADOC versus AC-DOC ≤ 0.63. An odds ratio of 0.63 corresponds, for instance, to a difference of 10% *v* 15% of pCR rates for ADOC and AC-DOC, respectively. Odds ratios greater than 0.63 (≤ 1) were defined to represent clinical noninferiority of ADOC. Power calculations were based on the results of an interim analysis of the GEPARDO trial,[10] in which the pCR rate for ADOC-treated patients was estimated to be 15%. Under the assumption of equal pCR rates of 15% in both treatment arms (odds ratio, 1), a sample size of 500 patients per arm is large enough to prove noninferiority of ADOC with a statistical power of 80% and at a significance level of 5%, using an one-sided exact test.

Two planned interim analyses were reviewed in a blinded fashion by an independent data monitoring committee (IDMC). A CI for the difference in pCR rates was calculated to confirm the assumptions of efficacy and to detect early any large differences in pCR rates. The confidence level of the interval was adjusted such that the overall significance level of 5% was maintained. The study was to be discontinued if the CI did not intersect with the region of equivalence, defined as a difference of ± 5% in pCR rates. In this case, a switch of hypothesis from noninferiority to superiority was designated.

According to the protocol, the primary efficacy end point was analyzed using an exact one-sided test at $\alpha = 5\%$. In addition, a 90% CI was calculated using normal approximation. To allow better comparison, the *P* value of the two-sided test ($\alpha = 5\%$) and the corresponding 95% CI were reported. 95% CI and the *P* values of a two-sided exact test were given for the secondary end points: breast clinical tumor response by palpation, tumor response by the most appropriate imaging method, nodal response, and breast-conserving therapy. For other end points, the rates were reported descriptively and grouped by treatment arm.

A prospectively planned, multivariate logistic regression model was used to determine the probability of pCR as a function of treatment group and various prognostic factors: age (≤ 50 *v* > 50 years); greatest tumor size measured by palpation (≤ median maximum diameter *v* > median maximum diameter); tumor grade (1 and 2 *v* 3); hormone receptor status (positive *v* negative); and clinical nodal status (negative *v* positive). This was performed only in patients for whom this information was available. To assess to what extent palpation, sonography, mammography, or MRI directly before surgery can predict a pCR, we calculated conditional relative frequencies on the basis of all patients for whom the specific method had been applied to estimate predictive values.

RESULTS

Patients and Baseline Results

This multicenter study was performed at 77 centers in Germany. From June 1999 to September 2001, 913 of 1,000 planned patients were enrolled. Enrollment ended prematurely in accordance with the recommendation of the IDMC after review of the second planned interim analysis of 395 patients, which occurred in September 2001. Among all patients enrolled, 455 were randomly assigned to ADOC and 458 were randomly assigned to AC-DOC; the flow of patients through the study is illustrated in Figure 1.

The full analysis population consisted of 904 patients: 451 were treated with ADOC and 453 were treated with AC-DOC. The safety population consisted of 903 patients (one patient without safety data for an unknown reason was excluded). The primary end point analysis was performed on 885 patients (full-efficacy population; Fig 1).

The median age at random assignment was 51 years (range, 24 to 77 years); 57.4% of the patients were peri- or postmenopausal. Diagnosis was ascertained using core-cut needle biopsy in 98% of the patients and by incisional biopsy in 2% of the patients. As the most appropriate tumor imaging method, sonography was specified in 764 patients (84.5%), breast MRI was specified in 55 patients (6.1%), and mammography was specified in 85 patients (9.4%). Most baseline characteristics were well balanced in the two treatment arms except nodal status and progesterone receptor status (Table 1).

Compliance With Treatment

Of the full analysis population (Fig 1), 763 patients (ADOC, n = 415 [92.4%]; AC-DOC, n = 348 [76.8%]) received all planned cycles of chemotherapy. Among patients randomly assigned to AC-DOC, one patient received a total dose of 100 mg docetaxel and one patient received only three cycles of AC. Treatment was stopped early in 136 patients (ADOC, n = 34 [7.5%]; AC-DOC, n = 102 [22.6%]). Reasons for discontinuation included toxicity/adverse event (ADOC, n = 25; AC-DOC, n = 57), request of patient/lack of compliance (ADOC, n = 11; AC-DOC, n = 43), disease progression (ADOC, n = 4; AC-DOC, n = 10), death (AC-DOC, n = 2), and other causes (ADOC, n =1; AC-DOC, n = 9). The toxicities leading to discontinuations were fever/infection (ADOC, n = 9; AC-DOC, n = 11) including febrile neutropenia (ADOC, n = 3; AC-DOC, n = 4), bone marrow suppression (ADOC, n = 2; AC-DOC, n = 15), skin changes (ADOC, n = 4; AC-DOC, n = 10), hypersensitivity reaction (ADOC, n = 1; AC-DOC, n = 5), mucositis (ADOC, n = 1; AC-DOC, n = 3), neuropathia (ADOC, n = 1; AC-DOC, n = 2), thromboembolism (ADOC, n = 1; AC-DOC, n = 2), and other severe adverse events (ADOC, n = 6; AC-DOC, n = 9), which occurred in fewer than three patients.

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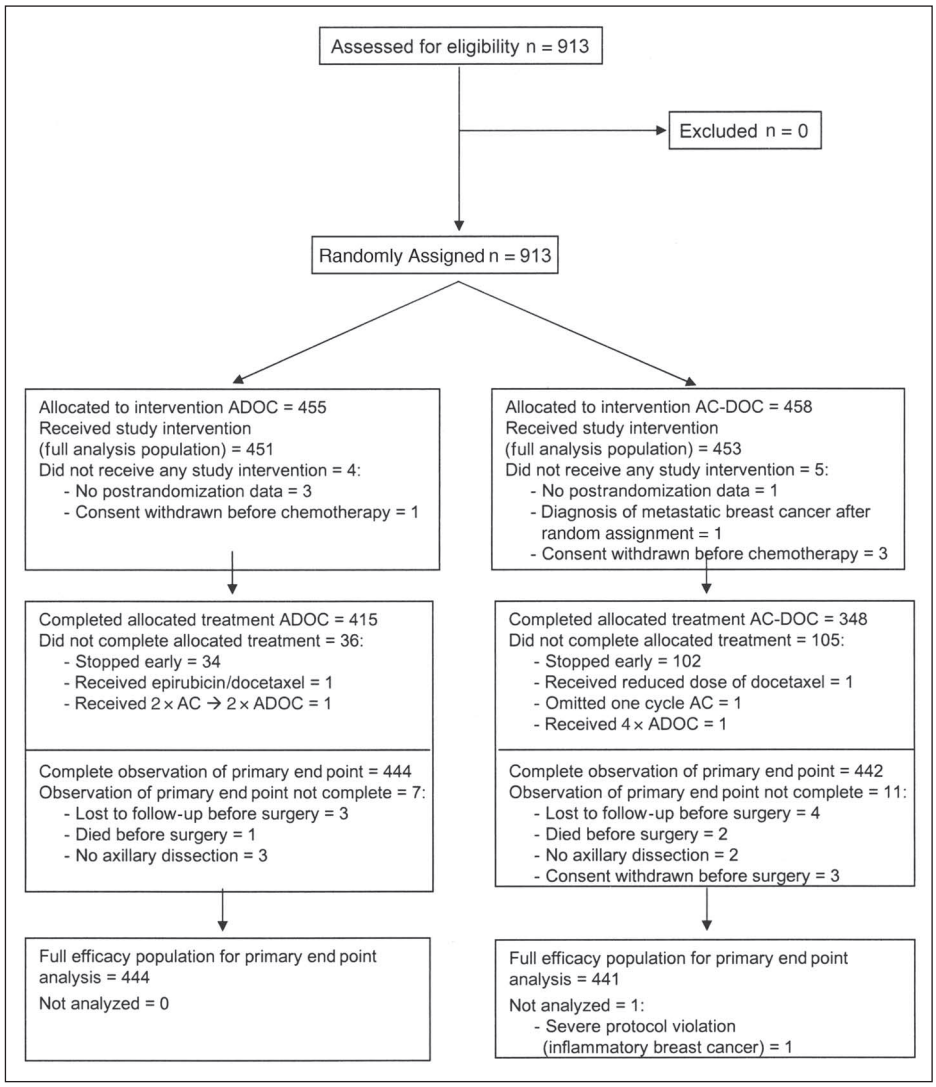

Fig 1. Progress of patients through the study. AC-DOC, sequential schedule of doxorubicin and cyclophosphamide followed by docetaxel; ADOC, docetaxel in dose-dense combination with doxorubicin.

Efficacy

The results of the second interim analysis calculated the conditional probability for noninferiority of ADOC to be less than 1% and AC-DOC was likely to be superior to ADOC.[14] On this basis, the IDMC made a recommendation and the trial steering committee decided to stop recruitment of the trial and to switch the hypothesis from noninferiority of ADOC to superiority of AC-DOC.

In total, 94 patients (10.6%) of the full-efficacy population had a pCR in all resected specimens of the breast and axilla. It is significant that twice as many patients achieved pCR with AC-DOC (14.3%; n = 63) than with ADOC (7.0%; n = 31), yielding an odds ratio of 2.22 (90% CI, 1.52 to 3.24; one-sided $P < .001$; 95% CI, 1.41 to 3.49; two-sided $P < .001$). Overall, 103 (11.6%) patients had a pCR of the primary breast tumor (grade 4 pathologic response), with twice as many patients achieving pCR with AC-DOC (15.9%; n = 70) than with ADOC (7.4%; n = 33). An additional 44 patients (5.0%) had a grade 3 pathologic response (residual in situ tumor only). Among these patients, 16 (3.6%) were treated with ADOC and 28 (6.4%) were treated with AC-DOC. Therefore, a clinically meaningful pathologic response (grades 3 and 4) of the primary tumor was achieved in 16.6% of patients (ADOC, 11.0%; AC-DOC, 22.3%; Table 2).

Prediction of pCR

In the multivariate logistic regression analysis, three variables were predictive of pCR: treatment assignment, tumor grade, and hormonal receptor status, with odds ratios of 2.42, 3.72, and 3.23, respectively (Table 3). Using a backward selection procedure (selection level 10%), the same variables remained significant predictors of response to chemotherapy.

Tumor Regression by Palpation and Imaging Methods

On the basis of the full-efficacy population, a total of 16 patients were excluded from this analysis because of

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Table 1. Baseline Characteristics of Randomly Assigned Patients in Full Analysis Population

Characteristic	ADOC (n = 451) %	ADOC (n = 451) No.	AC-DOC (n = 453) %	AC-DOC (n = 453) No.
Age, years				
Median		52		51
Range		24-77		24-74
Menopausal status				
Premenopausal	41.7		43.5	
Peri-/postmenopausal	58.3		56.5	
Tumor size, mm				
Palpation				
Median		40		40
Range		10-160		15-150
Most appropriate imaging method				
Median		30		29
Range		13-110		9-200
Tumor size by palpation, cm				
0.0-1.9	0.7		0.9	
2.0-3.0	41.2		38.6	
3.1-4.0	26.9		28.4	
4.1-5.0	15.7		17.2	
> 5.0	15.7		15.0	
Not assessed	0.9	4	1.1	5
Tumor size by most appropriate imaging method, cm				
0.0-1.9	6.0		8.0	
2.0-3.0	52.8		51.9	
3.1-4.0	26.6		25.4	
4.1-5.0	6.0		7.1	
> 5.0	8.7		7.7	
Positive nodal status by palpation	37.8		42.4	
Not assessed	0.2	1	0	0
Positive nodal status by sonography	37.6		49.9	
Not assessed	1.6	7	0.4	2
Tumor grade				
I or II	61.0		62.6	
III	39.0		37.4	
Not assessed	13.5	61	13.9	63
Tumor type				
Ductal invasive	75.7		72.4	
Lobular invasive	15.6		15.7	
Other	8.7		11.9	
Not assessed	0.4	2	0	0
Estrogen receptor status				
Positive	65.3		69.5	
Not assessed	11.3	51	11.7	53
Progesterone receptor status				
Positive	61.9		55.1	
Not assessed	11.5	52	11.5	52

Abbreviations: ADOC, docetaxel in dose-dense combination with doxorubicin; AC-DOC, sequential schedule of doxorubicin and cyclophosphamide followed by docetaxel.

insufficient information on physical examination before or after chemotherapy.

Three hundred seventy-seven patients (43.4%) achieved a clinical CR detected by palpation after chemotherapy (ADOC, 31.2%; AC-DOC, 55.7%), and 319 (36.7%) achieved a clinical PR (ADOC, 44.0%; AC-DOC, 29.3%). The overall local tumor response rate using palpation was significantly higher among AC-DOC patients compared with ADOC patients (two-sided $P < .001$). Overall, stable disease was observed in 143 patients (16.5%), occurring in 21.6% of those treated with ADOC and in 11.3% with AC-DOC. Disease progression or the occurrence of a new lesion was detected in a total of 30 patients (3.5%), with 14 patients (3.2%) in the ADOC arm and 16 patients (3.7%) in the AC-DOC arm (Table 2).

Table 2. Primary and Secondary End Point Response Rates

Response	ADOC No.	ADOC %	AC-DOC No.	AC-DOC %	Odds Ratio	95% CI	Two-Sided *P*
Primary end point: pCR (n = 885)							
pCR: Breast tumor and lymph nodes	31	7.0	63	14.3	2.22	1.41 to 3.49	< .001
						1.52 to 3.24*	< .001*
Grade 4 pathologic response in breast tumor	33	7.4	70	15.9			
Grade 3 pathologic response in breast tumor	16	3.6	28	6.4			
Histologically negative lymph nodes	246	55.4	267	60.5	1.24	0.95 to 1.61	.13
Secondary end points							
cRR (n = 869)	328	75.2	368	85.0	1.86	1.32 to 2.62	< .001
iRR (n = 863)	297	68.6	338	78.6	1.68	1.24 to 2.29	< .001
cNR (n = 428)	138	72.3	208	87.8			
iNR (n = 393)	110	62.5	175	80.7			
NR (n = 401)	100	54.6	164	75.2	2.52	1.65 to 3.85	< .001
BCT without need for reconstruction (n = 883)	257	58.1	279	63.4	1.25	0.96 to 1.64	.11
BCT (n = 885)	292	65.8	331	75.1	1.57	1.17 to 2.10	< .005

Abbreviations: ADOC, docetaxel in dose-dense combination with doxorubicin; AC-DOC, sequential schedule of doxorubicin and cyclophosphamide followed by docetaxel; pCR, pathologic complete response; cRR, response rate detected by palpation; iRR, response rate detected by best imaging method; cNR, nodal response detected by palpation; iNR, nodal response detected by sonography; NR, nodal response detected by palpation and sonography; BCT, breast conservation therapy.
*90% CI for pCR and one-sided *P* value for pCR according to primary statistical hypothesis.

Within the full-efficacy population, sonography as the most appropriate imaging method was undertaken before chemotherapy in 745 patients and was repeated after chemotherapy in 720 patients (81.4%). Mammography was chosen as the most appropriate imaging method before chemotherapy in 85 patients. MRI was initially administered prior to chemotherapy to 55 patients and was repeated after chemotherapy in 46 patients (5.2%). Thus, tumor response was assessed on the basis of 863 patients for whom the same imaging technique before and after chemotherapy was used.

A CR determined using the most appropriate imaging method was achieved in 38 ADOC patients and 102 AC-DOC patients. The overall local tumor response rate detected by imaging was significantly higher among AC-DOC patients (78.6%) compared with ADOC patients (68.6%; two-sided $P < .001$; Table 2).

Sonography, when administered before surgery, had high specificity (90.3%) compared with palpation (61.7%; Table 4); nevertheless, sonography was less sensitive (60.5%) than palpation (81.6%). Neither palpation nor any of the imaging techniques employed to assess tumor response was associated with a meaningful positive predictive value for pCR of the breast tumor.

Response of Axillary Lymph Nodes

A total of 879 patients of the full-efficacy population could be analyzed for nodal response and were classified into two groups: patients with lymph nodes initially suggestive of disease, as assessed by palpation or sonography

Table 3. Significant Predictors of pCR Identified From Multivariate Logistic Regression Analysis

Variable	pCR No.	pCR %	Odds Ratio	95% CI	*P*
Therapy (n = 885)					
AC-DOC	63	14.3	2.42	1.42 to 4.08	.0011
ADOC	31	7.0			
Tumor grade (n = 765)					
3	62	21.4	3.72	2.13 to 6.45	.0001
1 or 2	26	5.5			
Hormone receptor status (n = 783)					
Negative	47	22.8	3.23	1.91 to 5.46	.0001
Positive	36	6.2			

Abbreviations: pCR, pathologic complete response; ADOC, docetaxel in dose-dense combination with doxorubicin; AC-DOC, sequential schedule of doxorubicin and cyclophosphamide followed by docetaxel.

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Table 4. Sensitivity and Specificity of Palpation and Imaging Methods Before Surgery for Predicting pCR

Complete Response According to Each Method	Sensitivity		Specificity		Positive Predictive Value (%)	Negative Predictive Value (%)
	No. True Positive	%	No. True Negative	%		
Palpation (n = 869)	84	81.6	473	61.7	22.3	96.1
Sonography (n = 732)	52	60.5	583	90.3	45.2	94.5
Mammography (n = 81)	6	50.0	59	85.5	37.5	90.8
Magnetic resonance imaging (n = 50)	3	60.0	39	86.7	33.3	95.1

Abbreviation: pCR, pathologic complete response.

before systemic therapy (50.5%), and patients for whom both results were negative (49.5%).

Regarding the two treatment arms, 45.0% of patients (198 of 440) in the ADOC arm and 56% (246 of 439) in the AC-DOC arm were diagnosed with lymph nodes initially suggestive of disease. Although the portion of patients with evidence for initially involved lymph nodes was higher in the AC-DOC group, result of axillary palpation after systemic therapy was more often negative after AC-DOC (87.8%) than after ADOC (72.3%).

Sonography showed similar results: after systemic therapy, there were more patients without lymph nodes suggestive of disease after AC-DOC (80.7%) than after ADOC (62.5%; Table 2). After chemotherapy, lymph nodes that were initially enlarged before treatment were no longer detectable (NR) in 65.8% of patients (ADOC, 54.6%; AC-DOC, 75.2%).

Breast Conservation Surgery

The rate of breast conservation surgery, irrespective of the need of further reconstruction, was higher among patients receiving AC-DOC compared with patients treated with ADOC (two-sided $P < .005$; Table 2). A similar but less significant trend in the rate of breast conservation surgery without reconstruction was observed among patients from both treatment arms.

Toxicity

The most common WHO grade 3 to 4 hematologic toxicities (> 5% in frequency) were leucopenia (ADOC, 53.7%; AC-DOC, 74.2%) and neutropenia (ADOC, 44.7%; AC-DOC, 66.4%). The incidence of febrile neutropenia was less than 5%, arising in only 21 AC-DOC patients (4.6%; 14 during AC, six during docetaxel, and one with separate episodes of febrile neutropenia during both AC and docetaxel) and 14 ADOC patients (3.1%). The most common WHO grade 3 to 4 nonhematologic toxicity was alopecia, occurring in more than 90% of patients in both treatment arms (Table 5). Additional events, which occurred in fewer than 5% of patients in either arm, were hypersensitivity reactions, thrombocytopenia, cardiac arrhythmia, neurotoxicity, and fluid retention. Three patients died during study treatment (two as a consequence of pulmonary embolism and one as a result of an unknown reason).

DISCUSSION

This is the first phase III trial comparing two different strategies for incorporating doxorubicin and docetaxel into the primary treatment of operable breast cancer. AC-DOC achieved significantly better results for all efficacy end points: pathologic and clinical response rate, nodal response rate, and rate of breast conservation. Because the two regimens differ in the number of agents, cycles, and weeks of treatment, any one of these variables could account for the superiority of AC-DOC. The improvement of efficacy was not associated with a clinically relevant increase in toxicity. Neutropenia was more common with the sequential treatment, but patients in this arm did not receive prophylactic granulocyte colony-stimulating factor, whereas ADOC-treated patients did. The incidence of febrile neutropenia was similarly low in both groups (AC-DOC, 4.6%; ADOC, 3.1%). Only the treatment compliance was superior with ADOC (92.4%) compared with AC-DOC (77.2%), which is likely because the dose-dense ADOC regimen could be completed in only 8 weeks compared with 24 weeks.

The pCR rate of 14.3% achieved with the sequential preoperative AC-DOC regimen is particularly impressive when one considers the conservative definition of pCR that was employed in this study, as well as the median tumor size at baseline.

The AC-DOC regimens used in the NSABP B-27[12] and the GEPARDUO trials are identical with regard to the doses of cytotoxic drugs and the simultaneous use of tamoxifen irrespective of hormonal receptor status. Therefore, a reasonable comparison of the results can be performed if the same definitions for pCR are used and the slightly more favorable risk profile is taken into account (T1 tumors with clinically positive axillary nodes were eligible in the NSABP trial). In both trials the AC-DOC regimen was superior to the comparator. The percentage of patients with no invasive

Table 5. Incidence (> 5%) of WHO Grade 3 and 4 Adverse Events (n = 903)

Treatment	ADOC		AC-DOC Full Sequence		AC/DOC Each Phase			
					AC		DOC	
	No.	%	No.	%	No.	%	No.	%
Hematologic toxicity*								
Leucopenia	240	53.7	336	74.2	228	50.3	278	66.3
Neutropenia	192	44.7	288	66.4	237	55.6	225	57.8
Thrombocytopenia	0	0.0	8	1.8	6	1.3	3	0.7
Nonhematologic toxicity								
Alopecia	408	91.1	421	93.3	401	88.9	393	94.2
Fatigue	127	28.3	100	22.2	47	10.4	80	19.2
Loss of appetite	77	17.2	61	13.5	31	6.9	43	10.3
Nausea, vomiting	45	10.0	66	14.6	57	12.6	18	4.3
Hot flushes	36	8.0	55	12.2	37	8.2	39	9.4
Constipation	18	4.0	39	8.6	22	4.9	24	5.8
Stomatitis	17	3.8	36	8.0	6	1.3	32	7.7
Diarrhea	34	7.6	18	4.0	4	0.9	16	3.8
Infections	27	6.0	16	3.5	7	1.6	9	2.2
Skin changes	13	2.9	32	7.1	5	1.1	29	7.0
Nail changes	4	0.9	23	5.1	1	0.2	22	5.3

Abbreviations: ADOC, docetaxel in dose-dense combination with doxorubicin; AC-DOC, sequential schedule of doxorubicin and cyclophosphamide followed by docetaxel.

*The incidence of febrile neutropenia was < 5% with ADOC (n = 14; 3.1%); AC- DOC (n = 21; 4.6%). Febrile neutropenia was defined as neutrophils WHO ≥ grade 3, fever WHO ≥ grade 2, and no simultaneous infection (WHO = 0).

breast cancer cells in the removed breast tissue after AC-DOC treatment was similar, with 26.1% and 22.3% in NSABP B-27 and GEPARDUO, respectively. Furthermore, four cycles of AC delivered during 12 weeks (the NSABP B-27 control arm) achieved a similar pathologic response as the 8-week ADOC regimen (13.7% and 11.0%, respectively). Comparable results were also reported for clinical and nodal response rates in both trials. However, whereas the rate of breast conservation surgery could not be improved with the sequential regimen in the NSABP B-27, there was a significant improvement in breast conservation with AC-DOC compared with ADOC in the GEPARDUO trial. In the trial described in this article, the surgeons may have taken more advantage of the observed decrease of tumor volume by resecting the breast tumor according to its new margins. A significant number of treatment discontinuations were observed with AC-DOC in both NSABP B-27 and GEPARDUO trials (21.1% and 22.6%, respectively); however, this may be caused not only by cumulative toxicities but also by limited patient compliance to the specific trial situation in which shorter treatments are randomly compared with longer treatments.

Two other phase III trials have explored sequential neoadjuvant regimens containing anthracycline plus taxane. The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) trial[15] compared a dose-dense sequence of three cycles of epirubicin followed by three cycles of paclitaxel with four 3-week cycles of a combination of both drugs. The interim analysis of 475 patients showed a statistically superior rate of disappearance of all invasive tumor cells of 18% *v* 10% for the sequential regimen, with higher total doses but the same treatment duration of 12 weeks. The European Cooperative Trial in Operable Breast Cancer[16] compared two postoperative chemotherapy regimens versus four cycles of a preoperative AC plus paclitaxel combination followed by four cycles of cyclophosphamide, methotrexate, and fluorouracil (total duration, 32 weeks). The preoperative regimen was associated with disappearance of all invasive tumor cells in 23% of patients.

No benefit in efficacy but comparable toxicity was found for six courses of the simultaneous application of docetaxel with doxorubicin (AD) versus AC in 363 primary breast cancer patients. Twenty-three percent of the patients had inflammatory or locally advanced inoperable tumors and the median tumor size was 6 cm. No residual tumor cells in the removed breast tissue and axillary nodes were found in 12% (AD) and 16% (AC).[17] Again, the combination of AD did not lead to an improvement in locoregional response compared with AC. The potential impact on survival of three possible doxorubicin plus docetaxel combinations (AC-DOC, AD, and simultaneous ACDOC) is being explored currently in the NSABP B-30 trial.

The Aberdeen Breast Group[11] enrolled 162 patients with large tumors or locally advanced breast cancer and treated them with four cycles of preoperative cyclophosphamide, doxorubicin, vincristine, and prednisolone (CVAP). Responders (66.1%) were randomly assigned to four additional cycles of either CVAP or docetaxel, whereas

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nonresponders (34.1%) received docetaxel. CVAP followed by docetaxel was superior to CVAP-CVAP, with a complete disappearance of invasive tumor cells achieved in 30.8% and 15.4% of patients, respectively. Importantly, initially responding patients treated with CVAP followed by docetaxel had a significantly higher 5-year survival rate (90% *v* 70%) compared with those treated with CVAP-CVAP.[18]

However, after 68.8 months of follow-up of the NSABP B-27 study, the preoperative sequence of AC-DOC led only to a significantly better relapse-free survival but not to a better distant or overall survival, when compared with AC alone or with AC followed by postoperative docetaxel.[19] Patients from all treatment groups had a favorable long-term outcome when preoperative treatment resulted in a pCR. However, the higher number of patients with a pCR and improved outcome in the AC-DOC group could not sufficiently improve the overall treatment results in this group. Patients only gained a significant disease-free survival benefit from the preoperative application of docetaxel when they had achieved a partial clinical response to AC.

We found that apart from the regimen administered, high tumor grade and negative hormonal receptor status were significant predictors for attaining a pCR. Tumors that do not overexpress hormonal receptors have been shown in other studies to be more responsive to chemotherapy than hormone receptor–positive tumors[12,15,16]

To predict the probability of a pCR directly before surgery, neither palpation nor the applied imaging methods were sufficiently reliable to identify patients who did not need breast surgery. Sonography showed the highest positive predictive value and may be preferred for monitoring tumor response because of the possibility of repeat investigations and minimal inconvenience for the patient.

In conclusion, preoperative systemic treatment of primary operable breast cancer with eight courses of sequential AC-DOC significantly improves response for locoregional disease compared with four courses of dose-dense ADOC every 14 days. The AC-DOC regimen can be recommended as primary systemic treatment when a maximum locoregional tumor response is needed.

Authors' Disclosures of Potential Conflicts of Interest

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