Original article

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In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the GEPARTRIO pilot study

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Background: Response to the first two cycles of preoperative chemotherapy might differentiate subgroups of breast cancer patients with high or minimal chances for a pathologic complete response (pCR) and may be used as an *in vivo* chemosensitivity test.

Methods: Breast cancer patients were treated with two cycles of TAC (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 every 21 days). Patients whose tumors showed a response received four more cycles. Patients whose tumors did not respond were randomized to four additional cycles TAC or NX (vinorelbine 25 mg/m^2 days 1 and 8, capecitabine 2000 mg/m^2 days 1–14, every 21 days). The primary end point was pCR at surgery.

Results: Two hundred and eighty-five patients showed a clinical response, in 73.0% after two cycles, in 88.4% at surgery, and a pCR was seen in 17.9%. Breast conservation was possible in 72.2%. Responding patients obtained a pCR in 22.6% whereas non-responding patients reached a pCR in 7.3% and 3.1% with TAC or NX, respectively. Grade III/IV neutropenia and febrile neutropenia were observed during TAC in 70.2% and 13.5%, respectively. Significantly less toxicity were observed with NX.

Conclusion: Early response to TAC can reliably identify patients with a high chance of achieving a pCR. New effective treatments need to be explored for patients without an early response.

Key words: breast cancer, docetaxel, *in vivo* chemosensitivity test, preoperative

Introduction

Prediction of treatment effect might help to exclude patients with a low probability of a treatment benefit and improve the risk : benefit ratio in breast cancer patients. However, up to now all efforts have failed to find reliable predictors for response to cytotoxic treatment.

In our previous preoperative chemotherapy studies [1, 2] we investigated a set of clinical and biological markers that may have value in predicting a pathological complete response (pCR). 'Clinical response after two cycles of chemotherapy' was the only significant predictor in a multivariate analysis. Patients with at least a clinical partial remission after two cycles had a pCR rate of 17%, whereas patients with a tumor area reduction of <50% obtained a pCR rate of only 3%. We therefore generated the hypothesis that patients with suboptimal tumor response to a first treatment need and might benefit from a non-cross-resistant salvage chemotherapy regimen.

Currently, TAC (docetaxel, doxorubicin, cyclophosphamide) appears to be the most promising combination chemotherapy for node-positive, early-stage breast cancer. Only recently, this regimen has shown promising, preliminary survival advantages over 5-Fluorouracil/adriamycin/cyclophosphamide (FAC) [3]. We considered TAC as an appropriate first-line preoperative regimen in early-stage breast cancer.

Vinorelbine (N) and capecitabine (X) have meaningful single-agent activity in breast cancer. Both drugs have been explored in patients with taxane-resistant disease. Preclinical

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data suggest synergistic cytotoxic activity and a lack of cross resistance [4–6]. We have chosen the NX regimen as second-line treatment for patients in whom no clinical remission was elicited after two cycles of preoperative TAC.

Patients and methods

Objectives and end points

The primary aim of the study was to determine the pCR rate of four cycles of TAC and four cycles of NX as salvage treatment in patients whose tumors did not initially respond to two cycles of TAC as preoperative treatment for early-stage breast cancer. A pCR was defined as no microscopic evidence of residual viable tumor cells (invasive or non-invasive) in all resected specimens of the breast, irrespective of lymph node involvement.

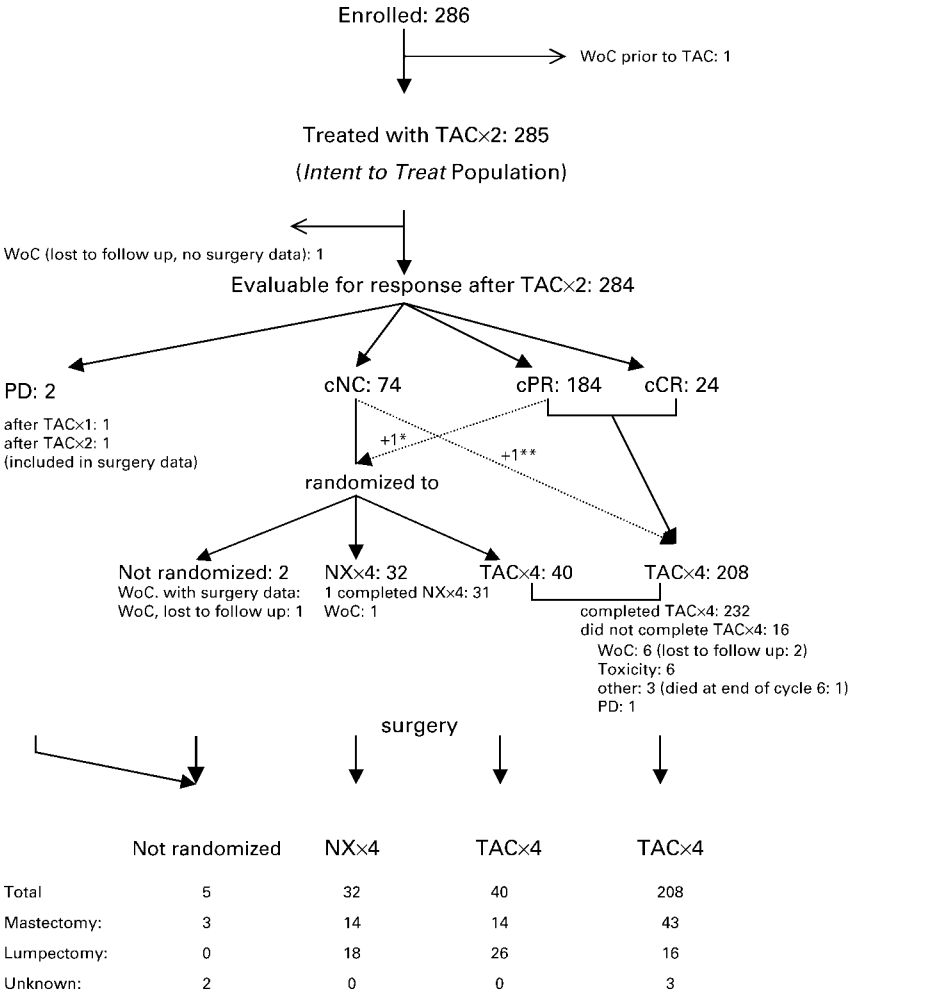
Secondary aims included determination of clinical response according to WHO criteria in the breast after TAC×2, the pCR rate after TAC×6 in patients whose tumors initially responded to TAC, the pCR rate in tumor subgroups, and safety according to National Cancer Institute Common Toxicity Criteria (NCI CTC).

Patient characteristics

Patients with previously untreated, unilateral or bilateral primary breast carcinoma could be enrolled in the study if they provided written informed consent. Diagnosis had to be confirmed histologically by core-cut biopsy. A breast tumor lesion had to be measurable in two dimensions by palpation, with one diameter of at least 2 cm. Bilateral mammography and breast ultrasound, a chest X-ray, abdominal ultrasound and/or computed tomography (CT) scan, and a bone scan were performed at initial screening. A tissue block of the core biopsy had to be made available for central Her2 measurement by fluorescence *in situ* hybridization (FISH). Other inclusion criteria were age 18 years or older, Karnofsky performance status of at least 80%, normal left ventricular ejection fraction, and sufficient hematopoetic, liver and renal function. Patients were excluded with evidence of distant metastasis, prior chemotherapy or radiation, previous serious illnesses, concurrent treatment with sex hormones or experimental drugs, known hypersensitivity reaction to the study compounds, or male gender.

Treatment

All patients were scheduled to two cycles of TAC (doxorubicin 50 mg/m^2 followed by cyclophosphamide 500 mg/m^2 and docetaxel 75 g/m^2, all on



	Not randomized	NX×4	TAC×4	TAC×4
Total	5	32	40	208
Mastectomy:	3	14	14	43
Lumpectomy:	0	18	26	16
Unknown:	2	0	0	3

WoC: withdrawal of consent, PD: progressive disease, cNC: clinically no change, cPR: clinical partial response, cCR: clinical complete response; TAC, docetaxel, doxorubicin, cyclophosphamide; WX, vinorelbine, capecitabine.

*clinical partial remission but falsely randomized as non-responder, **clinically no change, but falsely treated as responder

Figure 1. Distribution of patients throughout the study.

day 1, every 3 weeks). Supportive treatment consisted of dexamethasone 20 mg i.v. before docetaxel and 4 mg orally twice daily on days 2–4, ciprofloxacin 500 mg orally twice daily on days 5–10, and granulocyte colony-stimulating factor as treatment and secondary prophylaxis of febrile neutropenia or infection. Tumor response was determined by palpation during the third week of the second cycle. If the tumor showed a response, treatment was continued with four more cycles of TAC. If the tumor size decreased less than 50%, patients were randomized to either four more cycles of TAC or four cycles of NX (vinorelbine 25 mg/m^2 on days 1 and 8 plus capecitabine 1000 mg/m^2 orally twice/day on days 1–14, every 3 weeks). Patients with disease progression were removed from the study and treated at the discretion of the investigator.

The target lesion and regional lymph nodes were examined by palpation, and hematological and biochemical parameters were assessed every cycle. Mammography and a breast ultrasound were repeated at the end of the second cycle and before surgery. Within 21 days after completion of chemotherapy and after overall assessment of response, patients had to undergo surgery and postoperative treatment according to standard recommendations.

Statistics

According to our previous retrospective results we projected a pCR rate of 3% after TAC×4 in non-responding patients and estimated a pCR rate of 10% for the non-cross-resistant NX regimen. A sample size of 40 patients per arm would reach non-overlapping 80% confidence intervals using a one-sided Student's *t*-test. Assuming that 50% of tumors would not respond to TAC×2 and 5% of patients would be ineligible, the total sample size needed in the trial was 170. However, the observed rate of non-responders was lower than anticipated (28%), and the sample size was increased to 286 in order to obtain at least 80 non-responding patients. Randomization of non-responders was stratified according to participating center, operable or locally advanced tumor, and Her2-status (positive, negative or unknown, as centrally assessed by FISH. The analysis was planned on an intention-to-treat basis, including all patients who received at least one dose of study medication.

The protocol was reviewed by local ethics committees. Source data were verified independently in 100%. The conduct of the trial was supervised by an Independent Data Monitoring Committee.

Results

Baseline

The pilot phase of this trial was started in September 2001 with 23 centers in Germany, and enrolled 286 patients within 1 year. The distribution of patients throughout the study is shown in Figure 1.

Baseline patient characteristics are shown in Table 1. The median age for all patients was 50 years (range 24–74). Forty-three per cent of the patients were premenopausal. The median tumor size measured by palpation was 4.0 cm (range 1.2–20.0) and 2.8 cm (range 1.1–10.0) if measured by ultrasound. In five patients the tumor was clinically measured below 2 cm but sonographic measurement anticipated a much larger tumor size.

Compliance

In total, 1544 cycles of TAC and 122 cycles of NX were delivered. Two hundred and sixty-three (91.2%) patients received the planned six cycles of chemotherapy. Dose reductions of TAC were needed for hematological toxicities in eight patients, all at cycle 3 or later. Treatment was delayed for more than 6 days in 42 (2.7%) cycles, which was due to toxicity in 22 cycles. No dose reduction of vinorelbine was recorded. Capecitabine was discontinued on day 7 in one patient but that was for reasons unrelated to study treatment. Day 1 of NX was delayed for more than 6 days in six (5%)

Table 1. Patients' characteristics at baseline (intention-to-treat population) and after TAC×2

Parameter	Total population *n* (%) patients	TAC×6	TAC×4	NX×4
Total	285	208	40	32
Age (years)				
<40	39 (13.7)	26 (12.5)	7 (17.5)	5 (15.6)
40–60	174 (61.0)	125 (60.0)	23 (57.5)	22 (68.8)
60+	72 (25.3)	57 (27.5)	10 (25.0)	5 (15.6)
Tumor stage				
T1	5 (1.7)	5 (2.4)	0	0
T2	208 (73.0)	152 (73.1)	30 (75.0)	21 (65.6)
T3	41 (14.4)	29 (13.9)	5 (12.5)	7 (21.9)
T4	31 (10.9)	22 (10.6)	5 (12.5)	4 (12.5)
Axillary nodes				
Negative	152 (53.7)	110 (53.4)	23 (57.5)	16 (50.0)
Positive	131 (46.3)	96 (46.6)	17 (42.5)	16 (50.0)
Unknown	2	2		
Histologic subtype				
Ductal invasive	221 (77.8)	164 (78.8)	29 (72.5)	24 (77.4)
Lobular invasive	43 (15.1)	28 (13.5)	9 (22.5)	5 (16.1)
Other	20 (7.1)	16 (7.7)	2 (5.0)	2 (6.5)
Unknown	1			1
Histologic grade				
I	13 (5.3)	8 (4.5)	3 (9.1)	2 (7.1)
II	144 (58.8)	98 (54.7)	19 (57.6)	22 (78.6)
III	88 (35.9)	73 (40.8)	11 (33.3)	4 (14.3)
Unknown	40	29	7	4
Hormone receptor status				
ER+/PgR+	123 (47.9)	84 (44.7)	22 (57.9)	13 (50.0)
ER+/PgR-	34 (13.2)	27 (14.4)	3 (7.9)	4 (15.4)
ER-/PgR+	18 (7.0)	10 (5.3)	3 (7.9)	4 (15.4)
ER-/PgR-	82 (31.9)	67 (35.6)	10 (26.3)	5 (19.2)
Unknown	28	20	2	6
Her2 status (FISH)				
Negative	185 (70.9)	130 (68.1)	28 (75.7)	22 (78.6)
Positive	76 (29.1)	61 (31.9)	9 (24.3)	6 (21.4)
Unknown	24	17	3	4

TAC docetaxel, doxorubicin, cyclophosphamide; NX, vinorelbine, capecitabine; ER, estrogen receptor; PgR, progesterone receptor; FISH, fluorescence *in situ* hybridization.

Table 2. Efficacy end points of preoperative chemotherapy (intention-to-treat population)

Response	Clinical response after two cycles of chemotherapy		Clinical response before surgery		Pathologic response at surgery
	By palpation	By ultrasound	By palpation	By ultrasound	
Complete	24 (8.4)	1 (0.4)	120 (42.1)	29 (10.2)	51 (17.9)
Partial	184 (64.6)	130 (45.6)	129 (46.3)	134 (47.0)	10[a] (3.5)
No change	74 (26.0)	84 (29.5)	23 (8.1)	39 (13.7)	219[b] (76.8)
Progression	1 (0.4)	11 (3.9)	8 (2.8)	7 (2.5)	
Not evaluated	2 (0.7)	59 (20.7)	5 (1.8)	76 (26.7)	5 (1.8)

[a]Residual carcinoma *in situ* only.
[b]Residual invasive carcinoma present.

cycles. This was due to toxicity in four cases. Delivery of vinorelbine was never delayed for more than 6 days.

Response evaluation after TAC×2

Two hundred and eighty-five of 286 patients enrolled received at least one dose of TAC (intention-to-treat population). Among these, 284 were evaluable for response after TAC×2. A clinical complete response (cCR) within the breast was detected in 24 (8.4%) and a partial response in 184 (64.6%) of the patients, resulting in an overall response rate of 73.0%. Stable disease was found in 74 (26.0%) and two patients had progressive disease at cycle 1 and cycle 2 (Table 2). The median diameter of the tumors decreased to 2.4 cm (range 0–12).

Breast ultrasound after TAC×2 was performed in 226 patients and median tumor diameter was 1.8 cm (range 0.5–7.0). Overall tumor response was detected by ultrasound in 46%, of which 85.4% also showed a response by palpation. Clinical tumor response was confirmed by breast ultrasound in 68.3% of cases.

Preoperative evaluation of response

A total of 280 patients were assigned to receive four more cycles of chemotherapy after TAC×2. Seventy-two patients with stable disease were randomized to NX ($n=32$) or additional TAC ($n=40$). The imbalance of the size of the group resulted from the stratification by participating center and the low number of non-responding patients per center. In addition, the risk profile between the two groups was slightly imbalanced, with a tendency for more small, node-negative, receptor-negative and undifferentiated tumors in the TAC group (Table 1). Two hundred and eight patients with clinical response to TAC×2 were assigned to receive four more cycles of TAC.

Overall clinical response was found in 249 (88.4%) patients prior to surgery (Table 2). The cCR rate in responding patients was 50.5%. In initially non-responding patients treated with TAC and NX the rate was 22.5% and 21.9%, respectively. The median tumor size before surgery measured by palpation was 1 cm (range 0–7.5). In responding patients the median size was 0 cm and in non-responding patients treated with TAC or NX the median size was 2.0 cm or 2.4 cm, respectively.

Among all patients, breast conserving surgery was possible in 206 (72.2%); for those with operable tumors breast conservation was possible in 201 (79.1%) cases. In five (16.7%) patients with locally advanced disease, breast conserving surgery could be done. In patients responding to two cycles of TAC the rate was 86.3%, and in non-responding patients 66.0%.

Pathological evaluation

A pCR was found in 51 (17.9%) patients, and in 10 patients (3.5%) only residual carcinoma *in situ* was found (Table 2). If patients with operable tumors are considered, the pCR rate was 19.8%, whereas in locally advanced disease a pCR could be obtained in only 6.7%. Only three patients with a pCR showed histologically an involvement of the axillary nodes.

Patients responding to TAC×2 obtained a higher pCR rate of 22.9%, [confidence interval (CI) 17.6% to 30.0%] than non-responding patients further treated with TAC×4 (7.3%, CI 1.5% to 19.9%) and NX×4 (3.1%, CI 0.1% to 16.2%).

Breast ultrasound elicited a more accurate prediction of response. Thus pCR rates were 27.9% in patients responding to TAC×2 versus 5.3% in non-responders.

Analysis of factors for predicting pCR

The value of various clinical and histological parameters in predicting pCR was analyzed by univariate and multivariate regression analyses (Table 3). Clinical and sonographic response after TAC×2, histologic grade, and hormonal receptor status were significant predictors in a univariate model. The highest odds ratio was obtained for sonographic response evaluation (odds ratio 8, $P<0.0001$).

Patients with hormone receptor positive tumors, clinically not involved axillary nodes, tumor size smaller than 5 cm, grade 1 or 2, and older than 35 years ($n=38$) showed a very low pCR rate (2.6%). Patients with receptor negative tumors achieved a pCR rate of 26.7%. Patients with steroid hormone receptor negative tumors and a sonographic response after

Table 3. Univariate and multivariate regression analyses for parameters for predicting a pathological complete response

Variable (total no.)	Value	Univariate regression model			Multivariate regression model		
		Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Clinical response to TAC×2	Response vs Stable disease	5.2	2.0–14.9	0.002	1.1	0.3–4.3	0.9
Sonographic response to TAC×2	Response vs Stable disease	8.0	3.0–21.0	<0.0001	22.3	2.7–181.4	0.004
Age	≤50 years vs >50 years	1.6	0.9–2.9	0.1	1.4	0.3–5.8	0.6
Menopausal status	Premenopausal vs Postmenopausal	1.1	0.6–2.1	0.7	0.9	0.2–3.5	0.9
Clinical tumor size	0–40 mm vs >40 mm	1.8	0.9–3.4	0.08	3.1	1.1–9.0	0.03
Clinical nodal status	Negative vs Positive	1.1	0.6–2.0	0.8	1.4	0.6–3.5	0.4
Histologic grade	3 vs 1 or 2	0.4	0.2–0.7	0.004	1.2	0.4–3.2	0.8
Histologic subtype	Ductal vs Lobular/other	1.0	0.5–2.1	0.9	0.9	0.2–3.1	0.8
Extend of disease	Operable vs Locally advanced	2.2	0.6–7.6	0.2	1.8	0.2–19.7	0.6
Her2 status	Positive vs Negative	0.9	0.4–1.8	0.7	1.3	0.5–3.5	0.5
Hormone receptor status	Negative vs Positive	4.9	2.5–9.5	<0.0001	5.0	1.7–14.8	0.003

TAC: docetaxel, doxorubicin, cyclophosphamide; CI, confidence interval.

two cycles of TAC showed a pCR rate of 47.3%. pCR was similar in patients with or without Her2 positivity (18.4%).

In the multivariate model, only sonographic response after TAC × 2 and the hormonal receptor status were statistically significant.

Toxicity

Seventy-four per cent of the patients were still in excellent health after termination of chemotherapy; 18.5% had a slight decrease and 6.9% of the patients had an impaired performance status of <80%.

The most common grade 3/4 toxicity observed with TAC was neutropenia in 70% of the patients (Table 4). Febrile neutropenia was diagnosed in 13.5% of the patients and severe infection without neutropenia in 2%. Other frequent grade 3/4 toxicities were asthenia (17.1%) and nausea (7.5%). Two hundred and six serious adverse events were reported during TAC. One patient died suddenly of unknown reason during the third week of the sixth TAC cycle. Patients treated with NX developed grade 3/4 neutropenia in 34.4% of cases, and five serious adverse events were reported.

Discussion

This is the first report on the efficacy of the three-drug combination TAC as preoperative treatment of breast cancer. The pCR rate was 17.9% in the whole population including operable and non-operable disease, and 19.8% in patients with operable tumors. This is one of the highest pCR rates reported for a combination regimen in a multicenter trial [6a]. Other trials exploring combination regimens, such as AC [7], epirubicin-paclitaxel [9] and adriamycin–docetaxel [1, 2, 9] reported pCR rates ranging from 7.7% to 15.0%. However, eligibility criteria, as well as the definitions of a pCR, varied from one trial to another.

Trials reporting pCR rates similar to that in the present study employed sequential regimens. AC followed by docetaxel was studied in the NSABP-B27 [9] and GEPAR-DUO [2] trials and achieved pCR rates of 18.7% and 16.1%, respectively. Sequential regimens including paclitaxel led to similar pCR rates of 18% in the ECTO trial [10] as well as in the interim analysis of the German AGO trial [8]. These entire regimens were given to the patients over a period of at least 24 weeks, while the duration of TAC was only 18 weeks.

In general, the safety profile of TAC allowed the application of full dose in 93% of the patients. The most common severe toxicity was neutropenia. These results are comparable to the previous TAC trials, except that the rate of febrile neutropenia was reported with 24.7% in the BCIRG 001 trial. In contrast, 23.2% of patients discontinued the sequential AC and docetaxel regimen in the GEPAR-DUO study.

The early assessment of response after two cycles of chemotherapy provides reliable information about primary resistance to chemotherapy. In this study, tumor size decreased more than 50% after TAC × 2 in 73.0% of all patients. Patients with an early response to chemotherapy had higher pCR rates than non-responders (22.9% versus 5.5%). If tumor assessment is performed by ultrasound, one can predict even more accurately a group of non-responding patients (42.0%) with a similar low pCR rate of 5.3%, whereas the pCR rate in the group of sonographically responding patients is 32.1%. However, the best method in predicting a pCR remains controversial and needs to be evaluated on larger populations [12].

The design of the Aberdeen study [13] also contained an *in vivo* chemosensitivity test. Patients ($n = 159$) were treated with a doxorubicin-containing regimen for four cycles

Table 4. Comparison of maximum toxicity in 285 patients treated with TAC and NX

Symptom [*n* (%)]	Max NCI CTC grade	TAC (*n* = 252) cycles 1–6	TAC-NX (*n* = 33) cycles 1–6	TAC (*n* = 248) cycles 3–6	NX (*n* = 32) cycles 3–6
Anemia	1–2	234 (92.9)	24 (72.7)	213 (85.9)	23 (71.8)
	3–4	4 (1.6)	0	3 (1.2)	0
Thrombocytopenia	1–2	95 (37.7)	10 (30.3)	68 (27.4)	1 (3.1)
	3–4	2 (0.8)	1 (3.0)	2 (0.8)	0
Leucopenia	1–2	26 (10.3)	11 (33.3)	28 (11.3)	20 (62.5)
	3–4	212 (84.1)	22 (66.7)	184 (74.2)	7 (21.8)
Neutropenia[a]	1–2	18 (7.1)	4 (12.1)	22 (8.9)	14 (43.7)
	3–4	177 (70.2)	25 (75.6)	145 (58.5)	11 (34.4)
Febrile neutropenia	1–2	21 (8.3)	0	12 (4.8)	0
	3–4	34 (13.5)	4 (12.1)	21 (8.5)	2 (6.2)
Infection without neutropenia	1–2	82 (32.5)	7 (21.2)	58 (23.3)	3 (9.3)
	3–4	2 (0.8)	0	2 (0.8)	0
Nausea	1–2	173 (68.7)	21 (63.6)	160 (64.5)	11 (34.4)
	3–4	19 (7.5)	2 (6.1)	13 (5.2)	1 (3.1)
Vomiting	1–2	96 (38.1)	8 (24.2)	80 (32.2)	2 (6.2)
	3–4	8 (3.2)	1 (3.0)	5 (2.0)	1 (3.1)
Diarrhea	1–2	92 (36.5)	10 (30.3)	71 (28.6)	7 (21.9)
	3–4	12 (4.8)	2 (6.1)	8 (3.2)	2 (6.2)
Stomatitis	1–2	185 (73.4)	20 (60.6)	162 (65.3)	13 (40.6)
	3–4	13 (5.2)	0	9 (3.6)	0
Dysphagia/esophagitis	1–2	101 (40.1)	10 (30.3)	80 (32.2)	5 (15.6)
	3–4	2 (0.8)	1 (3.0)	2 (0.8)	0
Conjunctivitis	1–2	123 (48.8)	16 (48.5)	107 (43.1)	11 (34.4)
	3–4	5 (2.0)	0	5 (2.0)	0
Allergic reactions	1–2	51 (20.2)	6 (18.2)	34 (13.7)	4 (12.5)
	3–4	2 (0.1)	0	0	0
Edema	1–2	86 (34.1)	9 (27.3)	80 (32.2)	8 (25.0)
	3–4	9 (3.6)	0	8 (3.2)	0
Fluid retention	1–2	44 (17.5)	2 (6.1)	42 (16.9)	2 (6.2)
	3–4	3 (1.2)	1 (3.0)	2 (0.8)	1 (3.1)
Asthenia	1–2	181 (71.8)	28 (84.8)	176 (71.0)	24 (75.0)
	3–4	43 (17.1)	2 (6.1)	36 (14.5)	2 (6.2)
Alopecia	1–2	249 (98.8)	33 (100)	248 (100.0)	31 (96.9)
Hand–foot syndrome	1–2	42 (16.7)	8 (24.2)	37 (14.9)	6 (18.7)
	3–4	2 (0.8)	2 (6.1)	2 (0.8)	2 (6.2)
Nail	1–2	115 (45.6)	13 (39.4)	109 (44.0)	11 (34.4)
	3–4	2 (0.8)	0	1 (0.4)	0
Dyspnoea	1–2	72 (28.6)	11 (33.3)	62 (25.0)	8 (25.0)
	3–4	8 (3.2)	0	8 (3.2)	0
Sensory neuropathia	1–2	137 (54.4)	23 (69.7)	119 (48.0)	20 (62.5)
	3–4	6 (2.4)	0	5 (2.0)	0

[a]Measured only in 277 patients.

TAC, docetaxel, doxorubicin, cyclophosphamide; NX, vinorelbine, capecitabine; NCI CTC, National Cancer Institute Common Toxicity Criteria.

preoperatively. After 12 weeks of treatment, patients showing a clinical response (68%) were randomized to either four more cycles of the same regimen or four cycles of docetaxel. The change to docetaxel increased the clinical response rate after eight cycles from 68% to 94% and the pCR rate from 16% to 34%. However, in this study a broader pCR definition was used and cases with small foci of residual invasive disease were also included.

These results are in concordance with findings from the Royal Marsden Hospital, where the 'clinical response after two cycles of various chemotherapy regimens' of 198 patients with locally advanced tumors was the only independent predictor in multivariate analysis [14].

The aim of the present study was to evaluate the pCR rate TAC and NX in non-responding patients. If a large difference in pCR rates without overlapping confidence intervals occured, any further exploration of the two regimens within a phase III trial was to be stopped. However, the observed difference was small and to rule out or rule in the possibility that one treatment is superior to the other without imbalance in group sizes and prognostic characteristics warrants further accrual in the GEPARTRIO phase III study.

Inclusion criteria of current clinical trials allow the treatment of postmenopausal patients with a tumor clinically as small as 2 cm, non-involved axillary nodes and positive steroid receptor status with anthracyclines and taxanes, which would currently be considered in many cases as an over-treatment. The results of the multivariate analysis of this trial, as well as other studies, show that patients with hormone receptor expressing tumors have a significantly lower chance of achieving a histological complete response compared with patients with receptor-negative tumors [10, 11]. This chance decreases even more if other favorable tumor characteristics are present. In these patients the use of preoperative chemotherapy reaches pCR rates of only 2.6% and appears to be of no benefit to the patients.

Patients with receptor-negative tumors can be considered as the best candidates for preoperative chemotherapy treatment. This treatment can be reconfirmed if a sonographic response after the first two cycles of chemotherapy can be achieved. A pCR can be than expected in up to 50%.

We also prospectively assessed the predictive value of amplification of the *Her2* gene for the effect of an anthracycline–taxane combination therapy. Patients with or without *Her2* amplification showed the same clinical response and pCR rates. Therefore we could not confirm any predictive value of *Her2* in this prospective study design.

Other factors, e.g. assessing drug-efflux pumps, microtubule-associated parameters or apoptotic markers, which might potentially predict better the response to a taxane-based treatment, have not been assessed so far in this or other larger prospective studies. A comparison of such a molecular tumor characterization with the here proposed '*in vivo*' assessment needs to be performed in future studies.

Survival data available for the Aberdeen trial showed that switching to docetaxel in patients responding to doxorubicin can improve the outcome significantly, whereas patients without a response had the highest incidence of tumor relapses and deaths. The results of this trial support the hypothesis that patients without an early response to chemotherapy have chemoresistant disease and may not benefit from further cytotoxic treatment. However, a retrospective analysis from France with a long-term follow-up of 272 patients showed that patients without a response to three chemotherapy cycles appears to have a better survival if they reached a response to a second, non-cross-resistant chemotherapy, comparable to those with a clinical response upfront [15].

In the current phase III GEPARTRIO trial, not only are patients without an early response to TAC randomized to further TAC or NX, but also patients with an early response are randomly assigned to a further four or six cycles of TAC. It appeared to be appropriate to study further the duration of cytotoxic treatment in this group of chemosensitive tumors. The trial is estimated to reach the planned recruitment of 2014 patients in May 2005.

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