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In Vivo Chemosensitivity-Adapted Neoadjuvant Chemotherapy (Docetaxel–Doxorubicin–Cyclophosphamide Followed by Vinorelbine–Capecitabine Salvage Therapy) in Patients with Primary Breast Cancer: Results of the GEPAR-*TRIO* Randomized Pilot Study

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ABSTRACT*

Background and objectives: Tumor response during the first 2–3 cycles of chemotherapy for primary breast cancer provides valuable information on the likelihood of achieving pathologic complete response (pCR = no invasive or in situ tumor residuals). Non-responders to initial chemotherapy are less likely to have pCR and their prognosis is poor. We prospectively assessed neoadjuvant chemosensitivity of the tumor in vivo and evaluated treatment of non-responders with a salvage regimen.

Patients and methods: Chemotherapy-naïve patients with operable (T2–3, N0–2) or locally advanced (T4a-d, N0-3) breast cancer were first treated with 2 cycles of TAC (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 Day 1, q3 weeks). In the event of no palpable tumor (CR = complete response) or a tumor reduction of >49% (PR = partial response), 4 more cycles of TAC were administered (TAC6). Non-responding patients were randomized to either an additional 4 cycles of TAC (TAC2+4) or 4 cycles of NX (vinorelbine 25 mg/m^2 Day 1 + 8, capecitabine 2000 mg/m^2 Day 1–14, q3 weeks) (TAC–NX). Endpoints were pCR rates (primary) and clinical response at surgery, toxicity, compliance, surgical outcome, and the rate of PR/CR after 2 cycles of TAC.

Results: From October 2001 to September 2002, 286 (254 operable, 32 inoperable) patients were enrolled (median tumor size, 4.0 cm). CR+PR after 2 cycles of TAC was 73.1%. Just prior to surgery the CR rate was 43.2% in total (51.0%, TAC6; 20.0%, TAC2+4; 21.9%, TAC–NX). pCR rate was 18.4% in total (23.0%, TAC6; 7.3%, TAC2+4; 3.1%, TAC–NX). In a further 10 patients (4.9%) treated with TAC6, only in situ tumor residuals were found. Breast conservation was possible in 73.5% of patients in total (79.4%, TAC6; 61.0%, TAC2+4; 56.2%, TAC–NX). Grade III–IV neutropenia was the most frequent toxicity (71.4%, TAC; 75.8%, TAC–NX; 33.3%, NX). During NX treatment, grade III nonhematologic toxicity occurred in <6% of patients with no grade IV toxicity. Treatment was discontinued in 24 patients (8.4%) in total and due to toxicity in only 6 patients (2.1%).

Conclusions: TAC appears to be a highly effective preoperative treatment for breast cancer with moderate toxicity. Salvage therapy with NX is particularly well tolerated. Response after 2 cycles can identify patients with a high or minimal chance of achieving a pCR and could be used to assess in vivo chemosensitivity of the tumor.

*This poster contains updated data, which differ from the abstract.

INTRODUCTION

The main objectives of preoperative (neoadjuvant) chemotherapy for breast cancer are downstaging of the primary tumor prior to surgical resection – thus increasing the likelihood of greater breast conservation – and arrest of the systemic spread of micrometastatic disease. Docetaxel (Taxotere®) is one of the most active agents in breast cancer and clinical studies have shown that it is highly effective in the neoadjuvant setting, either as monotherapy or in combination with other agents.[1–4] In one Phase II study, weekly neoadjuvant docetaxel monotherapy resulted in an overall response rate (ORR) of 68% and a pathologic complete remission (pCR) rate of 16%.[1] Preoperative docetaxel plus doxorubicin (Adriamycin®) gave an ORR of 93% and significantly reduced primary tumor size by approximately 50% in one study[2] and gave an ORR of 81%, a pCR rate of 10% and a breast conservation rate of 69% in another study[3] (with or without simultaneous tamoxifen). Furthermore, interim data from the randomized GEPAR-DUO Phase III trial showed that both a neoadjuvant dose-dense 2-weekly schedule of docetaxel–doxorubicin and a neoadjuvant sequential schedule of doxorubicin–cyclophosphamide followed by docetaxel are effective approaches.[4]

The prognosis of patients with breast cancer who do not respond to the first 2–3 cycles of neoadjuvant chemotherapy remains poor. The present prospective, randomized, multicenter, Phase II pilot study comprised an in vivo chemosensitivity test (to initial treatment with 2 cycles of neoadjuvant docetaxel–doxorubicin–cyclophosphamide [TAC]) and explored the effectiveness of a neoadjuvant salvage regimen (vinorelbine–capecitabine [NX]).

OBJECTIVES

Primary objective

- pCR rate of (i) 4 cycles of TAC and (ii) 4 cycles of NX as neoadjuvant salvage therapy for patients who did not respond to 2 cycles of neoadjuvant TAC.

Secondary objectives

- Toxicity and compliance with TAC–NX
- Clinical response rate for the initial 2 cycles of TAC
- pCR rate of 6 cycles of TAC in responding patients.

Other objectives

- pCR rate in the subgroup of HER-2-positive and -negative patients (detected centrally by fluorescence in situ hybridization [FISH]).

METHODS

Main inclusion criteria

- Histologically confirmed (by core or Tru-Cut biopsy) unilateral or bilateral breast cancer
- Previously untreated operable (T2–3 N0–2 M0) or locally advanced (T4a–T4d N0–3 M0) breast cancer
- At least one bidimensionally measurable breast tumor (by palpation, mammography, ultrasonography, or magnetic resonance imaging); the largest lesion was measured in patients with multifocal or multicentric disease
- Age ≥18 years
- Karnofsky performance status ≥80%
- Normal cardiac function as evidenced by left ventricular ejection fraction (LVEF)
- Adequate hematologic, hepatic, and renal function
- Complete staging work-up within 3 months prior to study registration
- Written informed consent.

Study design and treatment

- Patients who fulfilled all the inclusion criteria were enrolled and treated as shown in Figure 1.

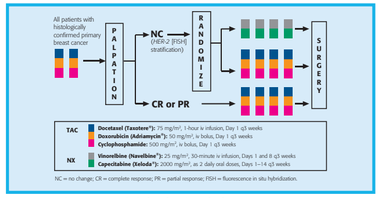

Figure 1. GEPAR-TRIO (pilot phase) study design.

- In the event of disease progression during the initial 2 cycles of TAC, patients were not randomized to further TAC or NX but were treated at the investigator's discretion.
- Prophylactic supportive therapy comprised:
  - dexamethasone 20 mg iv immediately before each docetaxel infusion and 4 mg po twice daily on Days 2 and 3 and once daily on Day 4 after chemotherapy
  - antiemetic (5-HT$_3$ antagonists) and antibiotic (ciprofloxacin or a suitable alternative) treatment for all patients.
- Prophylactic granulocyte colony-stimulating factor (G-CSF) was not permitted for the first treatment cycle but was allowed as curative treatment in the event of febrile neutropenia or infection and as prophylactic treatment for subsequent cycles (if there was a case of febrile neutropenia in a prior cycle).

RESULTS

Patients

- A total of 286 patients were enrolled into the pilot phase of the GEPAR-*TRIO* study.
- Baseline patient and tumor characteristics are summarized in Table 1.

CHARACTERISTIC	VALUE
Median age [range], years	50 [25–74]
Disease stage, n (%)	
Operable (T2–3 N0–2 M0)	254 (88.8)
Inoperable (T4a–Td N0–3 M0)	32 (11.2)
Karnofsky performance status, n (%)	
100	220 (76.9)
95	1 (0.4)
90	61 (21.3)
80	4 (1.4)
Tumor grade, n (%)	
1	13 (4.5)
2	144 (50.3)
3	88 (30.8)
Missing data	41 (14.3)
Tumor size, n (%)	
T1	5 (1.7)
T2	209 (73.1)
T3	41 (14.3)
T4	31 (10.8)
Median size [range], mm	40 [5–200]
Axillary nodal status, n (%)	
Negative	152 (53.1)
Positive	131 (45.8)
Missing data	3 (1.1)
Histologic type, n (%)	
Ductal invasive	222 (77.6)
Lobular invasive	43 (15.0)
Other	20 (7.0)
Missing data	1 (0.3)
Hormone receptor status, n (%)	
ER and PR negative	82 (28.7)
ER and/or PR positive	176 (61.5)
Missing data	28 (9.8)
***HER-2* (FISH) status, n (%)**	
Negative	185 (64.7)
Positive	76 (26.6)
Missing data	25 (8.7)

ER = estrogen receptor; PR = progesterone receptor; FISH = fluorescence in situ hybridization

Table 1. Baseline patient and tumor characteristics (n=286)

Treatment and response data

- In total, 262 (91.6%) patients completed the protocol-planned treatment (6 cycles) and 24 (8.4%) patients discontinued treatment due to: tumor progression (3 patients), toxicity (6 patients), consent withdrawn (11 patients), and other reasons (4 patients).
- Clinical response data for the first 2 cycles of TAC are summarized in Table 2. Data were not available for 3 patients due to withdrawal during the 2 cycles of TAC. One patient showing response withdrew after completing 2 cycles of TAC.

RESPONSE	NO. OF PATIENTS (%)
Overall response rate (ORR)	208 (73.5)
Complete response (CR)	24 (8.5)
Partial response (PR)	184 (65.0)
No change (NC)	74 (26.1)
Progressive disease (PD)	1 (0.4)

Table 2. Clinical response after 2 cycles of TAC (n=283)

- On the basis of the response data for the first 2 cycles of TAC, 207 patients received a further 4 cycles of TAC and 74 nonresponders were randomized to either 4 cycles of TAC (41 patients) or 4 cycles of NX (33 patients). Five patients were not randomized because of progressive disease (n=1) or missing data (n=4) (Figure 2).

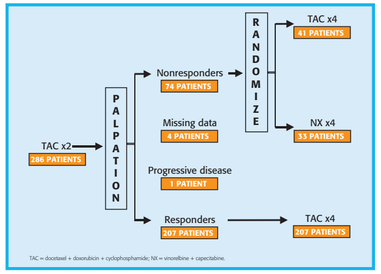

Figure 2. Summary of patient flow.

- Median tumor size at the time of randomization:
  - 20 mm (range: 0–120) for the TAC x6 (responders to initial 2 cycles of TAC)
  - 35 mm (range: 15–80) for the TAC x2 → TAC x4
  - 35 mm (range: 20–75) for the TAC x2 → NX x4.
- Clinical response data for all arms just prior to surgery are presented in Table 3.
- Pathologic response was evaluated in 278 patients – 51 (18.3%) patients had a pCR (no invasive or in situ tumor residuals) and 10 (3.6%) patients had only in situ tumor residuals (Table 4).

	NO. OF PATIENTS (%)			
	TAC x6	TAC x2 → TAC x4	TAC x2 → NX x4	TOTAL
Number of patients evaluated	207	41	33	281
Overall response rate (ORR)	199 (96.1)	30 (75.0)	20 (60.6)	249 (88.6)
Complete response (CR)	105 (50.7)	8 (19.5)	7 (21.2)	120 (42.7)
Partial response (PR)	94 (45.4)	22 (53.7)	13 (39.4)	129 (45.9)
No change (NC)	6 (2.9)	10 (24.4)	12 (36.4)	28 (10.0)
Progressive disease (PD)	2 (1.0)	1 (2.4)	1 (3.0)	4 (1.4)

Table 3. Clinical response data prior to surgery

	NO. OF PATIENTS (%)			
	TAC x6	TAC x2 → TAC x4	TAC x2 → NX x4	TOTAL
Number of patients evaluated	205	41	32	278
Patients with no invasive and no in situ tumor residuals (pCR)	47 (22.9)	3 (7.3)	1 (3.1)	51 (18.3)
Patients with in situ tumor residuals only	10 (4.9)	0 (0)	0 (0)	10 (3.6)
Patients with no invasive tumor residuals	57 (27.8)	3 (7.3)	1 (3.1)	61 (21.9)

Table 4. Pathologic response by treatment group

Prediction of response

- Patients who had a clinical response (assessed by palpation) during the first 2 cycles of TAC were more likely to achieve pCR at surgery (TAC x6 group in Table 4). Response data for pCR were unavailable for 8 patients.
- Patients with a high tumor grade (3 versus 1–2) and a negative hormone receptor status were also more likely to show a clinical response and pCR (Table 5).

	CLINICAL ORR AFTER TAC x2 (%)	pCR AT SURGERY (%)
Tumor grade		
1–2	68.4	13.1
3	81.8	28.4
ER/PR status		
Positive	68.4	10.6
Negative	82.9	36.6
***HER-2* status**		
Positive	71.6	16.7
Negative	78.4	18.9

ER = estrogen receptor; PR = progesterone receptor.

Table 5. Clinical overall response rate (ORR) and pathologic complete remission (pCR) rate by tumor grade, hormone status, and HER-2 status

Toxicity

- A total of 285 patients were assessable for toxicity. A summary of all National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3–4 hematologic and nonhematologic adverse events occurring in ≥5% of patients (on any arm) is provided in Table 6.

	NO. OF PATIENTS (%)			
TOXICITY	TAC x6 AND TAC x2 → TAC x4 (n=252) CYCLES 1–6	TAC x2 → NX x4 (n=33) CYCLES 1–6	NX x4 (n=32) CYCLES 3–6	TAC (n=248) CYCLES 3–6
Hematologic				
Leukopenia	212 (84.1)	22 (66.7)	7 (21.9)	184 (74.2)
Neutropenia	177 (70.2)[a]	25 (75.8)	11 (34.4)	145 (58.5)
Febrile neutropenia	34 (13.5)	4 (12.1)	2 (6.3)	21 (8.5)
Nonhematologic				
Asthenia	43 (17.1)	2 (6.1)	2 (6.3)	36 (14.5)
Stomatitis	13 (5.2)	0 (0)	0 (0)	9 (3.6)
Hand–foot syndrome	2 (0.8)	2 (6.1)	2 (6.3)	2 (0.8)
Diarrhea	12 (4.8)	2 (6.1)	2 (6.3)	8 (3.2)
Nausea	19 (7.5)	2 (6.1)	1 (3.1)	13 (5.2)

[a]Data available for 277 patients.

Table 6. Grade 3–4 hematologic and nonhematologic toxicities occuring in >5% of patients

GEPAR-*TRIO*: PHASE III UPDATE

- The enrollment of 2250 patients (by May 2005) is planned for the Phase III portion of the GEPAR-*TRIO* study
- As of 29 August 2003, a total of 981 patients (from 71 centers) had been accrued.

SUMMARY OF RESULTS

- Both neoadjuvant schedules (TAC x6 and TAC x2 → NX x4):
  - are feasible and showed moderate toxicity
  - gave high ORR (combined rate: 88.6%) and pathologic complete remission rates (18.3%).
- Patients who responded (assessed by palpation) to the initial 2 cycles of TAC were more likely to achieve pCR.
- High tumor grade and negative hormone receptor status were further predictors of good response.
- No significant difference in pCR rate was observed between TAC x4 or NX x4 as salvage therapy after neoadjuvant TAC x2.

CONCLUSIONS

- **Neoadjuvant TAC (docetaxel–doxorubicin–cyclophosphamide) is a highly effective treatment for primary breast cancer and responders to the initial 2 cycles are more likely to achieve pathologic complete remission.**

References

1. Estevez LG, Cuevas JM, Anton A, et al. Weekly docetaxel as neoadjuvant chemotherapy for stage II and III breast cancer: efficacy and correlation with biological markers in a phase II, multicentre study. Clin Cancer Res 2003;9:686–692.
2. Von Minckwitz G, Costa SD, Eiermann W, et al. Maximized reduction of primary breast tumor size using preoperative chemotherapy with doxorubicin and docetaxel. J Clin Oncol 1999;17:1999–2005.
3. Von Minckwitz G, Costa SD, Raab G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 2001;19:3506–3515.
4. Jackisch C, von Minckwitz G, Eidtmann H, et al. Dose-dense biweekly doxorubicin/docetaxel versus sequential neoadjuvant chemotherapy with doxorubicin/cyclophosphamide/docetaxel in operable breast cancer: second interim analysis. Clin Breast Cancer 2002;3:276–280.