Phase II Study of Neoadjuvant Gemcitabine, Pegylated Liposomal Doxorubicin, and Docetaxel in Locally Advanced Breast Cancer

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Abstract. *Aim: This was a phase II study to assess the activity of a novel neoadjuvant regimen in locally-advanced breast cancer. Patients and Methods: Fifty patients with histological confirmation of locally advanced breast cancer received treatment with gemcitabine 1000 mg/m^2 (day 1) followed by gemcitabine 800 mg/m^2 plus docetaxel 75 mg/m^2 plus pegylated liposomal doxorubicin (PLD) 30 mg/m^2 (day 8) every 3 weeks for at least 4 cycles, plus a final 2 additional cycles. Tumour size was T1 (n=2), T2 (n=32), T3 (n=14), T4 (n=2). All 50 patients underwent surgery. Results: Clinical complete, partial and no response were observed in 13 (26%), 24 (48%) and 11 (22%) patients, respectively (overall response rate: 74%). The number of chemotherapy cycles was found to be an independent predictor of a pathologic complete response. Conclusion: The combination of gemcitabine-docetaxel-PLD can yield high tumour response rates in patients with locally-advanced breast cancer who undergo a full treatment of 6 cycles.*

In the Western world, 15-20% of patients with breast cancer present with locally advanced disease at diagnosis, which is associated with a very poor prognosis (10-year survival: 20%-31%) if surgery alone is performed (1). The clinical implementation of primary chemotherapy appears to improve disease-free survival (DFS) and overall survival (OS) rates in breast cancer (2). As a consequence, neoadjuvant chemotherapy has been largely adopted as a treatment of choice for locally-advanced breast cancer as well as for other cancers (3-5). The principal endpoint of neoadjuvant treatment is tumour response because it positively correlates with long-term patient survival (6, 7). Anthracycline and taxane-based therapies are widely used in combination or sequential regimens, with pathological tumour response rates ranging between 22% and 31% (8, 9). The aim of the NSABP-27(10) trial was to determine whether the addition of docetaxel to doxorubicin-cyclophosphamide (AC) would increase DFS and OS in patients with operable breast cancer. Despite a doubling of pathological complete response (pCR) rate (26% *vs*. 15% AC alone), DFS and OS were not significantly improved with the addition of docetaxel to AC (10, 11). In a phase II study conducted in patients with locally advanced breast cancer, pegylated liposomal doxorubicin (PLD) 35 mg/m^2 in combination with paclitaxel showed an overall response rate of 71% and mild toxicity of the skin (3% hand-foot syndrome grade 3) (12). Gemcitabine is an effective agent for metastatic breast cancer (13), showing mild haematological toxicity when combined with taxanes (14-16). A recent phase II trial of gemcitabine-epirubicin-paclitaxel (GET) showed a 23% pCR rate, with mild toxicity (17). In this study, PLD, an anthracycline encapsulated in stealth liposomes, which are believed to efficiently deliver the doxorubicin within the tumour mass with less toxicity compared with standard doxorubicin formulation (18), was used. The study aimed to determine whether the combination of gemcitabine-PLD-docetaxel (GPT) would increase tumour response in patients with locally-advanced operable breast cancer.

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Patients and Methods

Patients with locally advanced breast cancer were eligible. Breast tumours were required on clinical-radiological evaluation to be T3 N1, T0-3 N2-2a, T4 a,b,c N0-3 or T4d. Diagnosis was obtained by

means of breast core biopsy. Inclusion criteria were the following: age >18 years; Eastern Cooperative Group (ECOG) performance status 0-2; measurable disease (as per radiological imaging); life expectancy >12 months; adequate haematologic blood profile; normal liver and kidney function; adequate cardiac function; no metastatic disease; negative pregnancy test (premenopausal women); and signed informed consent.

Before starting treatment, patients underwent blood exams (chemistry profile with complete blood count), chest and abdominal computed tomography (CT) scan, bone scan, basal bilateral breast magnetic resonance imaging (MRI) and cardiological assessment (including basal ejection fraction). The treatment schedule consisted of gemcitabine 1000 mg/m^2 on day 1 and 800 mg/^{2} on day 8; docetaxel 75 mg/m^2 on day 8; and PLD 30 mg/m^2 on day 8 with G-CSF (peflilgrastim 150 μg/19.2 MIU) on days 4, 10, 12 and 14. Treatment courses were repeated every 3 weeks, for 4 cycles. Gemcitabine was diluted in 250 ml of 0.9% saline solution and administered intravenously (*i.v.*) over 30 minutes. PLD was diluted in 5% dextrose 250 ml and administered intravenously over 60 minutes, and docetaxel was diluted in 250 ml of saline solution and administered as a 1-hour *i.v.* infusion; the agents were administered consecutively. All patients took vitamin B6 daily as prophylaxis for PLD-induced hand-foot syndrome. Patients were initially treated with 4 cycles of chemotherapy. Thereafter, tumour dimensions were assessed by physical examination and breast MRI, as required. If patients were responding to chemotherapy with tumour shrinkage >50%, they had 2 more cycles of chemotherapy, if not they were selected to undergo surgery. Tumour response was evaluated by pathological examination of surgical specimens of the breast and the omolateral axillary nodes.

The primary objective of the study was to evaluate tumour response in the primary breast cancer and in involved lymph nodes. The secondary objective was to evaluate tolerability of the regimen. Clinical and pathological response in the breast and axillary lymph nodes were assessed in all patients. At the end of chemotherapy, breast tumours were classified according to tumour response. The sum of major diameters of all target lesions (up to a maximum of 5 per organ and 10 in total) was used for assessment of objective response. Complete response (CR) was classified as disappearance of all target lesions. Partial response (PR) was classified as at least a 30% decrease in the sum of the largest diameter of target lesions from baseline. Progressive disease (PD) was classified as at least a 20% increase in the sum of longest diameter of target lesions using the smallest sum of the largest diameter recorded since treatment initiation or the appearance of one or more new lesions. Tumours which did not meet any of these classifications were considered as stable disease (SD). A complete pCR was defined as no residual tumour (only ductal carzinoma *in situ* (DCIS) was permitted and microinfiltration <2 mm in the breast and in the axillary lymph nodes). Pathological responses were graded according to the classifications proposed by Chevallier *et al*. (19) as follows: Grade 1, disappearance of all tumour on macroscopic or microscopic assessment; grade 2, presence of *in situ* carcinoma but no invasive tumour and no tumour in the lymph nodes; grade 3, presence of invasive carcinoma with stromal alterations; grade 4, few modifications of the tumoural appearance.

Treatment-related toxicity was assessed at each cycle. Left ventricular ejection fraction (LVEF) was assessed in each patient before starting chemotherapy. Toxicities were graded according to the WHO classification. Blood counts were performed on the first day of treatment: in case of granulocytopenia and/or thrombocytopenia on day 1, treatment was delayed until neutrophil count was >1500/μl and platelets >100,000/μl. G-CSF was administered prophylactically on day 3, 10, 12 and 14 to reduce the risk of granulocytopenia. To prevent hand-foot syndrome ice blocks were held in patients' hands during the PLD infusion (20). For grade 3 hand-foot syndrome, therapy was delayed until toxicity disappeared or regressed to grade 1. Glucocorticoid use was permitted (8 mg per day) until resolution of hand-foot syndrome. For other grade 3 toxicities, a 25% dose reduction of PLD was considered. All treatment was interrupted in the case of grade 4 toxicities. For mucositis, the same schedule used for skin toxicity was adopted for docetaxel. For adverse reactions to PLD (*e.g.* important/significant back pain immediately after drug administration) treatment was interrupted and then epirubicin was substituted for PLD.

Study design and statistical analysis. The number of patients to be enrolled in this phase II trial was calculated according to the Fleming's one-step study design (21), using the PASS statistical package (PASS 2002, NCSS, LLC, Kaysville, Utah, USA). The model was set up considering an alpha error of 5% and a power of 80%. The null and alternative hypotheses were considered a complete response rate of 50% and 75%, respectively (after 4 treatment cycles). Accordingly, a minimum total sample size of 44 patients was calculated to reject the null hypothesis and consider the treatment worth further investigation. The association between clinicopathological variables (estrogen receptor (ER)-alpha, progesterone receptor (PgR), Ki67, HER2, primary tumour pathological response, and axillary lymph node status at surgery) and tumour response was analysed by binary multivariable logistic regression, using the stepwise mode for the selection of variables significantly contributing to the prediction model. For this purpose, the SPSS statistical package was utilized (SPSS Base 16.0; SPSS Chicago, IL, USA).

Results

Between March 2005 and January 2007, a total of 52 patients were enrolled in the study. Fifty patients were evaluable for statistical analysis as one patient died of acute respiratory distress after treatment, and one patient decided to interrupt treatment after 3 cycles. Patient characteristics are described in Table I. Approximately one-third (34%) of patients had a T2 tumour with node involvement and one-third (33%) had T3-T4 tumour with node involvement. Two-thirds of patients (67%) had ER- and PR-positive tumours. Approximately one-third (38%) of patients had HER2-positive tumours based on FISH amplification and received trastuzumab in the adjuvant setting.

Tumour response. CR was observed in 26% of cases (95% CI: 15-41%) and a PR in 48% of cases (95% CI: 34-63%). The overall tumour response rate was 74% (95% CI: 59-85%; Table II). In the CR group, 8 of 13 patients had a pCR (16% of cases, 95% CI: 6-27%). In the PR group, 12 patients had residual tumour in the breast and axilla, and 12 patients achieved CR in the axilla but had residual tumour in the breast. The number of chemotherapy cycles significantly correlated with the number of CRs, as shown in Table III.

Table I. *Patients and tumour characteristics*.

	No. of patients (%)
Number of patients	52
Age (years), median (range)	51, 34-73
Menopausal status	
Pre	23 (44)
Post	27 (52)
Unknown	2 (4)
Baseline clinical stage	
T1-2 N0-1	15 (29)
T2 N2-3	18 (34)
T3-4 N0-3	17 (33)
Unknown	2 (4)
Oestrogen receptor status	
Positive	35 (67)
Negative	14 (27)
Unknown	3 (6)
HER2 status	
3+/FISH positive	20 (38)
Negative	28 (54)
Unknown	4 (8)

Table II. *Tumour response rate*.

	No. of patients (n=50 evaluable)	%	95% CI
Complete response	13	26	15-41%
Partial response	24	48	34-63%
Overall response	37	74	59-85%
Stable disease	11	22	12-36%
Progressive disease	2	4	0.5-14%
Not evaluable	2	4	0.5-14%
Pathological complete response	8	16	6-27%

Table III. *Correlation between number of cycles and clinical response rate*.

	Patients		
	4 Cycles	≥4 Cycles	Total
Complete response	1 (7%)	12 (34%)	13 (26%)
Partial response	8 (53%)	16 (46%)	24 (48%)
Overall response	60%	80%	74%
Stable disease	5 (33%)	6 (17%)	11 (22%)
Progressive disease	1 (7%)	1 (3%)	2 (4%)
Total	15 (30%)	35 (70%)	50 (100%)

Twelve patients who completed 6 cycles of therapy achieved a CR, and one patient who completed 4 cycles had a CR. Multivariate correlation analysis (conducted on 50 evaluable patients) showed that number of cycles completed was the only variable predicting complete tumour response (Table IV).

Toxicity. All enrolled patients maintained LVEF >50% and none met protocol-defined criteria for cardiotoxicity. Grade 3 and 4 hand-foot syndrome occurred in 12 and 2 patients, respectively (Table V). One patient had a grade 4 hand-foot syndrome after 5 cycles of therapy, which improved after 2 weeks, and that patient underwent surgery after 5 cycles and achieved 2 mm residual tumour in the breast and no tumour in the axilla (clinical stage was T3 N2a). During the first minute of the first PLD infusion, 9 (18%) patients had an allergic reaction defined as significant pain in the spine and a few minutes of hot flushes (Table V). They recovered with cortisone and antihistamine, discontinued PLD and were then administered epirubicin 75 mg/m^2. All 50 evaluable patients had grade 3 alopecia, and 4 (8%) patients had grade 3 mucositis, which was treated with an oral anti-fungal agent, with complete resolution. Treatment was delayed by 1 week in 4 patients because of grade 3 mucositis, which recovered to grade 1 or 0. One patient died after 2 cycles of chemotherapy because of adult respiratory distress syndrome that could not be clearly correlated to treatment. No cases of neutropenia were reported. Two patients had fever without neutropenia. They both had chest scans that revealed pneumonia, which recovered in 2 weeks. Treatment was delayed in these patients, and they were treated with appropriate antibiotics without a hospital admission.

Discussion

In this study the activity and tolerability of gemcitabine, PLD, and docetaxel was evaluated in the neoadiuvant setting for the treatment of women with locally advanced breast cancer. Studies investigating the optimal strategy of incorporating taxanes (up front in combination with anthracycline or following a regimen with anthracycline) showed a greater benefit in terms of pCR (22). Recently, in a study of 74 patients, Hamm *et al*. reported that 6 cycles of neoadjuvant gemcitabine plus epirubicin and paclitaxel every 21 days produced a 23% pCR rate (17). This combination was associated with a similar pCR rate as reported in the B-27 study (AC followed by 4 cycles of taxane) with 6 cycles instead of 8 cycles (pCR: 23 *vs*. 26%, respectively).

To explore the potential clinical benefits of different numbers of cycles, tumour response was evaluated after 4 cycles, and 2 more cycles were proposed to responding patients only. This treatment scheme was chosen to evaluate whether adding 2 more cycles might lead to higher tumour response rates in selected patients. Studies addressing the same issue have been recently published. Steger *et al*. reported that 6 cycles of epirubicin and docetaxel were superior to 3 cycles, with a pCR rate of 18.6% *vs*. 7.7%, respectively (p=0.00045) (23). In a

Table IV. *Factors predicting tumor response: multivariate logistic regression analysis.*

Variable	Beta value	SE	*p*-Value	95% CI
Age	–0.0948	0.118	0.4226	–0.327 - 0.137
Menopause	0.0939	2.509	0.9701	–4.824 - 5.012
Size	–0.7402	0.497	0.361	–1.714 - 0.233
ER	–0.0358	0.024	0.1406	–0.083 - 0.012
PR	0.0234	0.025	0.3414	–0.025 - 0.071
MIB1	0.1032	0.054	0.0540	–0.002 - 0.208
HER2				
0	–0.5497	1.684	0.7441	–3.850 - 2.750
1	–0.4847	1.714	0.7774	–3.845 - 2.876
2	–5.5707	2.827	0.0488	–11.112 -0.030
Cycles	2.9787	1.199	0.0130	0.629 - 5.329
Constant	–10.433	7.535	0.1662	–25.203 - 4.335

Table V. *Toxicity.*

Toxicity	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n
Anaemia	-	-	-	-
Neutropenia	5	2	-	-
Thrombocytopenia	-	-	-	-
Nausea	-	2	-	-
Vomiting	7	-	-	-
Diarrhoea	5	-	-	-
Constipation	1	2	-	-
Mucositis	3	11	3	-
Alopecia	-	-	50	-
Fatigue	12	-	-	-
Hand-foot syndrome	6	8	12	2
PLD reaction	9	-	-	
Pneumonia	-	-	2	

PLD, Pegylated liposomal doxorubicin.

randomised study, Reitsamer *et al*. showed that 6 cycles of epirubicin plus docetaxel achieved a 36% pCR rate compared with 10% with 3 cycles; pCR in axillary nodes was 52% *vs*. 45% with 6 *vs*. 3 cycles, respectively (p=0.045) (24). Considering all patients, the pCR rate in the current study was 26% (13/50). Overall, except for one patient, all patients who achieved a pCR received 6 cycles of chemotherapy. Among 50 evaluable patients, 35 received 6 cycles and one received 5 cycles of treatment; considering these 36 patients, 12 (33.3%) had a pCR and 16 (44.5%) had a PR. In contrast, out of 16 patients receiving 4 cycles, 1 (6.3%) and 8 (50%) patients experienced a complete and partial response, respectively. These findings strongly suggest that the identification of responding patients (as assessed by means of clinical assessment and breast MRI evaluation) could lead to tailoring treatment on an individual basis so to maximize the efficacy of a given chemotherapeutic regimen and spare unresponsive patients the toxicity of treatment. In light of these results, it is suggested that adding 2 cycles to the widely used 4-cycle regimen might increase tumour response rate in the neoadjuvant setting. On the other hand, a higher number of cycles does not appear to further increase the clinical benefit, as demonstrated in the GEPAR-TRIO trial: the dose intensification of chemotherapy showed that 8 cycles of docetaxel, doxorubicin, and cylophosphamide (TAC) did not yield higher response rates *versus* 6 cycles (25). pCR rates were not significantly different between the arms: 21.0% with 6 TAC cycles and 23.5% with 8 TAC cycles; 95% CI=–1.8% to 6.8%; p=0.27). In contrast, in the current study a 26% pCR rate following 6 cycles of therapy was observed (12).

Liedkte *et al*. have recently shown that patients with triple-negative breast cancer have increased pCR rates compared with those patients affected with non-triple negative tumours (26). In the Authors' experience, potential predictive factors such as ER, PR and HER2 expression and their combined negativity (triple-negative cases) had no statistically significant impact: however, the low statistical power (due to the small sample size of the study) cannot reliably rule out the importance of these biomarkers as predictors of response (26). Another issue in this field is the clinical significance of tumour response to neoadjuvant treatment in terms of patient survival. In light of these considerations, in the current study a pCR was considered as the clearance of invasive tumour both in the breast and in the axilla. Interestingly, it was observed that the number of chemotherapy cycles was an independent predictor of pCR. Therefore, it is hypothesized that the 6-cycle regimen might improve overall survival. These positive and encouraging results were not hampered by increases in relevant toxicities as shown in Table V. Therefore, 6 cycles of GPD can be considered a safe and tolerable outpatient treatment regimen.

In conclusion, the high overall response rates observed in the current trial support the use of 6 cycles as the standard regimen of neoadjuvant chemotherapy for locally advanced breast carcinoma. However, these findings must be confirmed in larger studies and improved survival has still to be proven after long term follow up, possibly within the frame of randomized controlled trials.

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