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RESEARCH ARTICLES

Doxorubicin and cyclophosphamide followed by weekly docetaxel as neoadjuvant treatment of early breast cancer: analysis of biological markers in a GEICAM phase II study

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Abstract
Introduction To evaluate the sequential administration of doxorubicin (A) and cyclophosphamide (C) followed by weekly docetaxel in women with stage II to IIIA breast cancer.
Patients and methods Patients received 60 mg/m^2 of A and 600 mg/m^2 of C every three weeks for four cycles followed by 12 infusions of weekly docetaxel at a dose of 36 mg/m^2 and with a 2-week resting period.
Results Sixty-three women were included. On an intention-to-treat basis, clinical response rate was 90% (95% CI: 83–98), with 46% complete responses. Breast-conserving surgery could be performed in 43 patients (68%). Complete pathological responses in the breast were confirmed in 17% of patients. No correlations between levels of expression of topoisomerase II alpha, survivin or p27 and the pathological response were detected. The study treatment was generally well tolerated.
Conclusion Neoadjuvant AC followed by weekly docetaxel is a feasible regimen for patients with early-stage breast cancer.

Keywords Anthracycline · Breast carcinoma · Primary chemotherapy · Sequential · Taxane · Weekly

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Introduction

The effectiveness of neoadjuvant chemotherapy (NC) with a combination of anthracyclines and alkylating agents, such as doxorubicin and cyclophosphamide (AC), has rendered it as one standard treatment for locally advanced breast cancer. More recently, very encouraging results have been obtained with the addition of taxanes into the neoadjuvant regimens. Docetaxel is considered to be one of the most potent compounds for the treatment of breast cancer [1]. In the neoadjuvant setting, docetaxel has a high response rate and tolerable toxicity profile when administered as single agent or in combination, either concurrently or sequentially [2–4]. Different randomised trials have reported that the addition of docetaxel to an anthracycline-based NC regimen enhanced clinical and pathological re-

sponse rates, especially when docetaxel was added sequentially [5–8].

Currently, much attention is devoted to determining the optimal schedule for administration of anthracyclines and docetaxel. The standard docetaxel regimen is of doses of 75–100 mg/m^2 given every three weeks. The most significant problem of this triweekly treatment is the high incidence of grade 3/4 haematological toxicities, notably neutropenia and febrile neutropenia [9, 10].

We have already carried out one of the first trials where weekly docetaxel was used as a single agent in the neoadjuvant treatment of early-stage breast cancer [11]. Results showed a high pathological response rate with a tolerable toxicity profile in which non-haematological toxicities were more common than haematological ones. In another study, which compared weekly vs. triweekly paclitaxel followed by an anthracycline/alkylating-based treatment [12], a significant improvement in efficacy was observed when the taxane was administered on a weekly schedule.

In an attempt to improve on these results, we have designed a prospective phase II study to evaluate the administration of triweekly AC followed by weekly docetaxel as neoadjuvant treatment for patients with operable breast cancer. Our primary objective was to determine the pathological complete response (pCR) rate. Other endpoints were to evaluate the clinical response and the safety of the treatment, and to determine any possible correlation between several molecular markers such as topoisomerase II alpha (Topo II), survivin and p27 and pathological response.

Patients and methods

Study design

This was a prospective, multicentre, open-label, phase II study performed in five hospitals in Spain. Recruitment of patients took place from February 2003 to May 2004. The Ethics Committee of each participating site approved the study protocol and all patients provided their written informed consent.

Selection of patients

The subjects selected for this study were women with previously untreated, histologically confirmed stage II or IIIA breast cancer. Histological samples were obtained through a trucut biopsy or an excision biopsy. Fine needle aspiration cytology (FNAC) was not considered acceptable. The presence of metastatic disease was excluded by bilateral mammography, chest radiography, an abdominal examination (computed tomography imaging or ultrasound) and a bone scintigraphy. Patients were ≥18 years old and had a Karnofsky index status ≥80%. Other inclusion criteria were adequate bone marrow (neutrophils ≥2.0×10^9/l, platelets ≥100×10^9/l and haemoglobin ≥10 g/dl) and renal and hepatic functions (creatinine ≤1.5×upper normal limit [UNL], or at least ≥60 ml/min of creatinine clearance; total bilirubin ≤1.0 mg/dl.UNL, aspartate aminotransferase [ASAT] and alanine aminotransferase [ALAT] ≤2.5×UNL and alkaline phosphatase ≤5×UNL). Patients with ASAT and/or ALAT ≤1.5×UNL associated with alkaline phosphatase >2.5×UNL were not included. A satisfactory cardiac function evaluated by electrocardiogram was also required. Left ventricular ejection fraction (LVEF) was performed only in case of suspected cardiac dysfunction and results had to be above the lowest normal limit at each site.

Patients were excluded if they had invasive bilateral tumour or if they had received previous treatment for breast cancer with immunotherapy, hormonal therapy, chemotherapy or radiotherapy. Other exclusion criteria included previous motor or sensory neurotoxicity ≥grade 2; other serious illness (such as congestive heart failure, angina pectoris, serious neurological or psychiatric disorders, uncontrolled infection, active peptic ulcer or unstable diabetes mellitus); previous malignancies (other than non-melanoma skin cancer, in situ cervical carcinoma, *in situ* ductal or lobular breast cancer or previous diagnosis of cancer with no evidence of disease for ≥10 years); contraindication for corticosteroid use; or pregnancy or lactation. Fertile women had to have a negative pregnancy test and be using an adequate non-hormonal contraception.

Chemotherapy regimen and other treatments

Patients received doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), both in a short intravenous infusion, every three weeks for four cycles (days 1, 22, 43 and 64). Three weeks later, docetaxel (36 mg/m^2) was administered as a 30-min intravenous infusion, weekly for six weeks (days 85, 92, 99, 106, 113 and 120) followed by a 2-week resting period (8-week cycle). After that, patients received a second docetaxel cycle (infusions on days 141, 148, 155, 162, 169 and 176). Adjuvant chemotherapy and radiotherapy were delivered according to the protocol of each participating centre. Hormonal treatment was started after the last chemotherapy infusion in all patients with positive oestrogen and/or progesterone receptor tumours and was continued for five years.

Patients received three doses of dexamethasone (8 mg), one the previous night, another one an hour before docetaxel infusion and the last one on the night of chemotherapy. Equivalent doses of other corticosteroids, such as prednisone or methylprednisone or prednisolone, were allowed. Premedication with anti-emetics was obligatory in all patients. Granulocyte colony-stimulating factor (G-CSF) support was only administered when neutrophil counts were below 1.5×10^9/l. Febrile neutropenia or severe infections (with or without neutropenia) during chemotherapy were treated with antibiotics and prophylaxis with G-CSF was also used if necessary in the remaining cycles.

Treatment modifications were allowed in the case of severe toxicity. If the neutrophil count fell to $<1.5\times10^9$/l or platelets $<100\times10^9$/l, chemotherapy was delayed, but continued upon recovery without any dosage modification. If toxicity persisted after day 35 for the AC treatment, or one week after docetaxel treatment, the patient was withdrawn from the study. Dosages of both drugs were reduced by 17% in the event of a second episode of febrile neutropenia, a second episode of severe infection (with or without neutropenia), mucositis ≥grade 3 or any other grade 3 toxicity. Patients were withdrawn from the study if evidence of toxicity did not improve after dosage reduction, or in the case of any grade 4 toxicities other than neutropenia or of a third episode of either a febrile neutropenia or a severe infection (with or without neutropenia).

Evaluation of safety and response

Pre-study evaluations included a medical history and physical examination, tumour measurements (mammography and echography), cardiac function tests, haematology and biochemistry tests, and other examinations as clinically indicated. Blood counts and serum biochemistry tests were repeated before each cycle and upon completion of the treatment schedule. Patients were asked to report the occurrence of any adverse experiences to the investigator. Toxicities were recorded and graded according to the Common Toxicity Criteria Version 2.0 from the Cancer Therapy Evaluation Program of the National Cancer Institute [13].

Tumour measurements were repeated before surgery, which was scheduled to take place within the four weeks following the final chemotherapy cycle. Clinical responses were assessed according to RECIST [14]. An overall response rate (ORR) was defined as any clinical response, either complete (CR) or partial (PR). The grade of pathological response was assessed in accordance with the Miller and Payne grading system [15]. pCR was defined as no evidence of invasive malignancy in the breast and lymph nodes (G5+D). The presence of carcinoma *in situ* was included in this description.

Molecular markers

Semiquantitative determination of three molecular markers was carried out by immunocytochemical methods. Tissue samples were taken prior to initiation of chemotherapy from the core of the primary tumours. Specimens were sent to a central laboratory for analysis of Topo II, survivin and p27. Paraffin-embedded tumours were processed with standard immunocytochemical techniques. As in previous studies [16], over-expression of Topo II was defined as >10% cells with nuclear staining. Tumours with more than 1% of cells with nuclear staining were considered to be over-expressing this protein. Lastly for p27, sections were scored according to the percentage of tumour cell nuclei with positive staining (1, <25%; 2, 25–75%; and 3, >75%).

Statistical analysis

Sample size was calculated using the Simon method in two steps. Taking into account a pCR of 12% achieved in previous studies with AC, we anticipated an improvement of up to 25% with the new schedule. With a type I error of 5% and a study power of 80%, 19 patients were needed in the first step and, if at least two pCR were found, up to 61 patients in the second step. At least 12 pCRs would support the hypothesis.

Associations between each of the molecular markers (Topo II, survivin and p27) with various baseline clinical variables (age, fertility status, histopathological type, histopathological grade and clinical stage) or to nodal status after chemotherapy were assessed using different statistical tests (Kruskal-Wallis, χ^2, Fisher exact and Mann– Whitney tests), depending upon the number of groups by which each variable was categorised and whether or not they followed a normal distribution. A multivariate analysis, by means of an ordinal logistic regression, was performed to assess the relationship between the pathological response of the primary tumour (dependent variable) and various independent variables (each of the previously mentioned baseline clinical variables, the pathological axillary lymph nodes response to chemotherapy and the molecular markers assayed). All efficacy and safety analyses were performed on the intention-to-treat (ITT) population. ORR and pCR were calculated with 95% confidence intervals (CI).

Results

Patients and disease characteristics at baseline

Sixty-three patients were enrolled in this trial. Baseline characteristics are summarised in Table 1. The majority of patients had an infiltrating ductal carcinoma (92%). One patient had stage I breast cancer at inclusion, however she was finally included in the analysis on an ITT basis.

Topo II was over-expressed in 33% of the tumours, although its expression could only be determined in 65% of them (49% of the assayed tumours were hence over-expressing Topo II). Survivin was positive in 29% of the tumours, being determined in 70% (hence 41% of the assayed tumours were positive for survivin). A reduction in nuclear immunolabelling of p27 was observed in 38% of the tumours, and was determined in 65% (hence 59% of the assayed tumours showed diminished nuclear labelling for p27).

Treatment administration

A total of 252 cycles of AC were administered, with a median of four cycles per patient (range: 4–4). Patients received 714 infusions of docetaxel with a median of 12 infusions per patient (range: 2–12). Most patients (87%)

Table 1 Patient and disease characteristics at baseline (*n*=63)

Characteristics	*N*	%
Age, years		
Median	48	
Range	25–80	
Karnofsky index		
100	55	87
90	8	13
Menopausal status		
Premenopausal	35	56
Postmenopausal	28	44
Tumour size (cm)		
Median	4.8	
Range	2.0–12.5	
Disease stage		
I	1	2
IIA	23	36
IIB	35	56
IIIA	4	6
Hormonal receptorsa		
ER+/PR+	32	51
ER+/PR–	18	28
ER–/PR+	3	5
ER–/PR–	10	16

[a]*ER*, oestrogen receptors; *PR*, progesterone receptors

Table 2 Clinical response rate on intention-to-treat basis (*n*=63)

Characteristics	*N*	%
Complete response	29	46
Partial response	28	44
Stable disease	5	8
Progressive disease	1	2
Overall response rate (95% CI)	57	90 (83–98)

Table 3 Correlation between molecular markers and pathological response in the breast

Number of pCR in the breast (%)	*p* value	
Topo II (*n*=41)[a]		
>10% nuclei ((*n*=20)	<10% nuclei (*n*=21)	
5 (12)	2 (5)	0.726
Survivin ((*n*=44)[a]		
>1% nuclei ((*n*=18)	<1% nuclei (*n*=26)	
5 (11)	3 (7)	0.268
p27 ((*n*=41)[a]		
<75% nuclei ((*n*=24)	>75% nuclei (*n*=17)	
6 (15)	2 (5)	0.196

[a]Number of patients for whom tumours could be assessed for the given molecular marker

completed treatment with AC and docetaxel, and the median relative dose intensity was 99% for both AC and docetaxel.

Eight patients (13%) could not complete treatment according to the study protocol due to unacceptable toxicity (*n*=6), progressive disease ((*n*=1) and consent withdrawal ((*n*=1).

Efficacy

Table 2 shows the clinical response rate assessed following completion of chemotherapy. On an ITT analysis, 29 patients (46%) showed a CR and 28 (44%) a PR for an ORR of 90% (95% CI: 83–98). Stable disease was achieved in 5 patients (8%) and the disease progressed in one patient (2%). Breast-conserving surgery could be performed in 43 patients (68%). Two patients could not undergo surgery because they were withdrawn from the study due to disease progression ((*n*=1) and unacceptable toxicity ((*n*=1). In another three patients (5%) the free margins of the excised tissue were histologically positive. A pCR, with no evidence of invasive tumour in breast (grade 5 by Miller and Payne criteria), was confirmed in 11 patients (17%, 95% CI: 8–27). Nine patients (14%, 95% CI: 6–23) had no malignant cells either in the breast or in the lymph nodes.

Predictive role of molecular markers

The level of expression for the molecular markers assayed (Topo II, survivin and p27) could not be associated with differences in clinical variables of the patients' population (age, fertility status, histopathological type, histopathological grade, clinical stage) or with the pathological response of the axillary lymph nodes to chemotherapy. Furthermore, the pCR of the primary tumour could not be predicted from the clinical parameters taken into account or from the molecular markers assayed (Table 3). Pathological response of axillary lymph nodes to chemotherapy showed a closer relationship with the pathological response of the primary tumour, but there was no statistical significance either in the multivariate analysis ((*p*=0.080) or if separately analysed (*p*=0.421).

Safety

The study treatment was generally well tolerated and there were no toxic deaths (Table 4). After AC, the most frequent grade 3/4 toxicities were neutropenia (16% of patients, 8% of cycles) and lymphopenia (10% of patients, 2% of cycles). Other severe toxicities after AC were vomiting (8% of patients, 3% of cycles) and leukopenia (6% of patients, 2% of cycles). Other severe toxicities during AC treatment were observed in fewer than 5% of patients. After docetaxel, the main severe toxicities were lymphopenia (41% of patients, 20% of infusions), leukopenia (8% of patients, 1% of infusions) and asthenia (8% of patients, 2% of infusions). Other severe toxicities were rare. Febrile neutropenia was only observed during AC administration in 3 patients (5%), one cycle each.

Six patients (9%) were withdrawn from the study due to toxicity including pancytopenia (*n*=1), bilateral pneumo-

Table 4 Incidence of grade 3/4 toxicity (*n*=63)

Toxicity	After AC, N (%)		After T, N (%)	
	Per cycle (*N*=252)	Per patient (*N*=63)	Per infusion (*N*=714)	Per patient (*N*=63)
Haematological				
Febrile neutropenia	3 (1)	3 (5)	0 (0)	0 (0)
Leukopenia	5 (2)	4 (6)	7 (1)	5 (8)
Lymphopenia	6 (2)	6 (10)	139 (20)	26 (41)
Neutropenia	19 (8)	10 (16)	1 (1)	1 (2)
Non-haematological				
Anxiety	0 (0)	0 (0)	1 (1)	1 (2)
CHF	0 (0)	0 (0)	1 (1)	1 (2)
Diarrhoea	0 (0)	0 (0)	1 (1)	1 (2)
Dry skin	0 (0)	0 (0)	1 (1)	1 (2)
Dyspnoea	0 (0)	0 (0)	2 (1)	2 (3)
Oedema	0 (0)	0 (0)	1 (1)	1 (2)
Asthenia	0 (0)	0 (0)	11 (2)	5 (8)
Hepatic dysfunction	2 (1)	1 (2)	4 (1)	2 (3)
Infection w/o neutropenia	1 (1)	1 (2)	1 (1)	1 (2)
Nausea	3 (1)	2 (3)	0 (0)	0 (0)
Syncope	1 (1)	1 (2)	1 (1)	1 (2)
Vomiting	8 (3)	5 (8)	0 (0)	0 (0)
Weight loss	0 (0)	0 (0)	1 (1)	1 (2)

CHF, congestive heart failure; w/o, without

nia ((*n*=1), congestive heart failure and dyspnoea ((*n*=1), hypersensitivity to docetaxel ((*n*=1), asthenia ((*n*=1) and facial oedema (*n*=1).

Discussion

We have presented here the results of a prospective multicentre phase II trial performed in women with stage II or II-IA primary breast cancer. Patients received four cycles of AC every three weeks followed by 12 weekly infusions of docetaxel (AC→T) as induction chemotherapy. Of 63 patients included, 17% had a pCR in the breast, and 14% a pCR in both the breast and the axilla. The majority of patients (90%) showed a clinical response, of which 46% were CRs.

Two previous phase III trials had tested a similar neoadjuvant schedule in operable breast cancer [5, 8]. In fact, they used the same doses and scheduling for AC as in the present study, but they differed in the manner of administration of docetaxel. In the GEPARDUO and NSABP B-27 trials, four cycles of docetaxel at a dose of 100 mg/m^2 every three weeks were given; whereas in this study, docetaxel at a dose of 36 mg/m^2 was infused once a week for six weeks in two 8-week cycles. In these studies, the pCR rate achieved in both the breast and the axilla ranged between 14% and 22%, and the ORR was between 85% and 91%, respectively. The results of the current study are in the lower part of the range of those mentioned, although it has to be taken into account that none of these phase III trials analysed their data on an ITT basis.

In another randomised trial that tested a similar NC regimen in operable breast cancer patients [7], the Aberdeen Group combined AC with vincristine and prednisolone (CVAP), which was administered every 3 weeks for four cycles. Thereafter, clinical responders were randomised to receive either another four cycles of 3-weekly CVAP or four cycles of 3-weekly docetaxel (100 mg/m^2). Non-responders were treated with four additional cycles of 3-weekly docetaxel. In an intention-to-treat analysis, they observed a pCR rate in the breast of 31% in the responder group and of 2% in the non-responder group; both groups were treated with CVAP→T. As in our study, both responders and non-responders were included for the scored pathological responses; we have recalculated the pCR rate for both of them and it was 16% (17 pCR in 107 patients), which is very similar to the 17% obtained in this study.

The pathological results obtained in this study are similar to those obtained in our previous study where weekly docetaxel was used as single agent in the neoadjuvant treatment of early-stage breast cancer (16%) [11], although the clinical response then was lower (68%) than with the current schedule (90%).

In terms of safety, the chemotherapy regimen of our study was well tolerated, with low myelosuppression rates (16% of patients with severe neutropenia and 5% with febrile neutropenia during AC) and no toxic deaths. The most frequent severe toxicity was lymphopenia (41%) and this was observed during docetaxel administration. The toxicity profile seems to be worse in the three phase III studies previously mentioned [5, 7, 8].

In this study, we attempted to find a positive correlation between the expression of the molecular markers Topo II, survivin and p27 and the pathological response obtained after NC with anthracyclines and taxanes. However, corre-

lations between any of those markers and pCR were not found. In previously reported studies, the over-expression of Topo II was associated with an improvement in disease-free survival (DFS) after an anthracycline-based chemotherapy [16–19], but this correlation could not be detected between Topo II and pCR after an anthracycline-based [20–22] or an anthracycline/taxane-based NC [23]. With regard to survivin, it has been reported that cells that over-express this protein may be more resistant to cytotoxic treatments [24] as it acts by inhibiting apoptosis [25, 26]. However, reported data referring to breast cancer are controversial [27–30]. Finally, the cyclin-dependent kinase inhibitor p27 depends on having a nuclear location to perform its cell cycle inhibitory function [31]. Thus, the exclusion of p27 from the nucleus would lead to a poor patient outcome in breast cancer [32]. However, some large studies did not support an independent role for p27 as a prognostic marker in breast cancer [33–35]. Unfortunately, the results obtained here do not further clarify the situation.

In summary, results from this phase II study have shown that NC with four cycles of AC every three weeks followed by 12 weekly infusions of docetaxel is an effective and safe schedule for treating patients with stage II and IIIA breast cancer. Similar efficacy outcomes were obtained in comparison with AC followed by triweekly docetaxel, although the toxicity profile appears to be better. However, a randomised comparison between both schedules will need to be performed in order to be able to draw a definite conclusion.

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Conflict of interest The authors have stated they do not have any conflict of interest that may inappropriately influence this work.

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