Phase II pilot study of weekly Docetaxel as Neoadjuvant Chemotherapy for operable Breast Cancer

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Abstract

Purpose: In this study of weekly docetaxel in the neoadjuvant treatment of stage II breast cancer, we evaluated the efficacy and safety of docetaxel and analyzed the correlation between the response observed and the expression of c-*erb*B2, ER status.

Patients and Methods: This study included patients with previously untreated, stage II & III breast cancer. Docetaxel was given as a 30-min i.v. infusion at a dose of 40 mg/m^2 weekly for 6 weeks, followed by 2 weeks rest. Patients received two 8-week cycles of treatment. Patients achieving a CR or partial response or who had stable disease at the end of treatment proceeded directly to surgery.

Results: A total of 40 patients were evaluated by intention-to-treat analysis for efficacy and safety. The overall clinical response rate was 65% (complete and partial response, 25 and 40%, respectively). Six patients (15%) achieved a pathological complete response. There was no correlation between response to docetaxel and the expression of molecular markers, however, the majority of the pathological complete responses were observed in patients with c-*erb*B2-negative tumors. Nonhematological toxicity was more common than hematological toxicity, with alopecia and asthenia were the most frequently reported adverse events. Severe hematological toxicity was rare.

Conclusion: Weekly docetaxel appears to be very effective in the neoadjuvant setting. A high pathological response rate was achieved with tolerable toxicity.

Introduction

Breast cancer is the most common cancer in women and it is incurable when metastases are diagnosed. Taxanes, namely docetaxel and paclitaxel, are effective chemotherapeutic agents in the metastatic, neoadjuvant and adjuvant settings. HER-2 over expression is detected in 25–30% of breast cancer , it confers aggressive tumor behavior as well as resistance to some systemic treatments and has been associated with poor outcome, in both node-negative and node-positive early breast cancer [1-4]. *In vitro*, HER-2 overexpression confers increased resistance to paclitaxel in breast cancer cells, while HER-2 degradation increases docetaxel-induced apoptosis [5-7]. This is further supported by data from a phase III clinical trial showing that paclitaxel response rate was significantly improved in breast cancer patients when HER-2 was downregulated by the humanized anti-HER-2 antibody, trastuzumab [8].

Neoadjuvant therapy for breast cancer generally refers to the administration of chemotherapy prior to local treatment with surgery and/or radiation. The biological rationale for neoadjuvant therapy of breast cancer is based on the observation of accelerated metastatic growth following tumor resection.. Neoadjuvant chemotherapy minimize the emergence of chemo resistant clones ,increasing tumor resectability by reducing the size of an unresectable tumor, improving local control and improving cosmesis by allowing breast-conserving treatment. It also offers an important test bed for novel therapies including new drugs and new combinations of drugs. More recently, neoadjuvant therapy has been studied as a way of testing the relevance of biological markers in predicting disease outcome. The expression of the proto-oncogenes c-*erb*B2 (*her2/neu*), *bcl-2* and *p53* have been evaluated as predictive markers in several trials without clearly defined results [9-12].

Observations from early studies, both single arm phase II studies and those randomizing pre-operative systemic therapy against post-operative adjuvant therapy, have confirmed that those women whose tumors have a pathological complete response to neo-adjuvant chemotherapy have the best long-term outcome, and this remains true after multivariate analysis [13]. It has even been suggested that regimens achieving a higher proportion of patients in pathological complete response should then be used in the adjuvant setting as they must give a survival improvement on older treatments [14].

The taxanes have emerged as critically important drugs in the treatment of patients with breast cancer. Taxanes were generally recognized as evidence-based components of therapy for metastatic breast cancer within a few short years of their initial phase II evaluations. In addition, the data in support of their use in the adjuvant and neoadjuvant settings continue to strengthen [15].

Docetaxel is a taxane prepared by semisysnthesis beginning with a precursor extracted from the needles of yew plant it binds to the ß-tubulin subunit causing inhibition of microtubule depolemerization [16], and several phase II and III trials reported a high activity in first- and second-line therapy of metastatic breast cancer, as well as in patients previously exposed or resistant to anthracycline [17-

18]. When docetaxel was compared with doxorubicin, it produced statistically superior response rates compared with doxorubicin (48% versus 33%, $P = 0.008$) and longer time to treatment failure [17]. It has also been studied in patients who have progressed on anthracycline-containing chemotherapy and differences in progression-free survival have been found [18].

Weekly regimens of taxanes may enhance dose intensity by minimizing regrowth of cells between cycles of treatment and can also be combined with other new drugs such as biological agents directed against the tyrosine kinase I receptor c-*erb*B2 [19] . Experience with docetaxel as neoadjuvant chemotherapy has mainly been in combination with an anthracycline . The rates of pahological complete remission (pCR) reported in these trials are similar to those obtained with standard regimens, although the best regimen with docetaxel as neoadjuvant chemotherapy has not yet been defined.

Based on indirect comparisons as well as the results of the recent randomized trial conducted in patients with metastatic breast cancer, docetaxel appears to be the more active taxane. In addition to its longer half-life, docetaxel also has a more rapid cellular uptake and longer intracellular retention than paclitaxel [20].. Docetaxel is highly active when given as a short, intermittent infusion. [21].

This study is a pilot phase II trial of single-agent docetaxel given on a weekly schedule as neoadjuvant treatment for patients with breast cancer. Our primary aim was to measure the overall objective clinical response rate to weekly docetaxel. Secondary objectives included assessing the safety of the regimen, measuring the pathological response rate to docetaxel, and evaluating the role of the c-*erb*B2 receptor and ER as potential predictive factors of response to single-agent docetaxel.

Patients and Methods

Patient Population

Patients with previously untreated, histologically confirmed, operable breast cancer were included in the study. Infiltrating disease was confirmed before chemotherapy for all patients. Patients were required to have measurable disease by physical examination and diagnostic breast imaging (mammogram, ultrasound and Magnetic Resonant Image) with a primary tumor ≥ 2 cm. All patients were ≥ 18 years. Patients had to have Eastern Cooperative Oncology Group performance status < 2, hemoglobin ≥ 10 g/dl, neutrophils ≥ 2×10^9/liter, and platelets ≥ 100×10^9/liter, with adequate hepatic and renal function (including calculated creatinine clearance ≥ 60 ml/min). Cardiac function was evaluated by echocardiography and a left ventricular ejection fraction of ≥50% was required. Patients were excluded if they had bilateral tumor or metastatic disease as confirmed by chest radiography, liver ultrasound or computer tomography imaging and bone scintigraphy, or if they had any other severe or uncontrolled systemic disease. Fertile women had to have a negative pregnancy test and had to be using adequate, non hormonal contraception.

Treatment

Docetaxel was given as a 30-min i.v. infusion at a dose of 40 mg/m^2 weekly for 6 weeks, followed by 2 weeks rest. Patients received two 8-week cycles of treatment. Patients achieving a CR or partial response or who had stable disease at the end of treatment proceeded directly to surgery. After surgery, adjuvant chemotherapy was delivered according to the standard regimen.

Docetaxel administration was delayed for up to 1 week in the event of a neutrophil count < 1×10^9/liter, platelet count <100×10^9/liter, or mucositis ≥ grade 2. If the toxicity had not recovered during this period, the patient was withdrawn from the study. The dose was reduced to 36 mg/m^2/week in the event of febrile neutropenia, mucositis ≥ grade 3, cutaneous toxicity (mainly acral erythema) ≥ grade 2, and all other grade 3 toxicities. Patients were withdrawn from the study in the event of an additional episode of febrile neutropenia or mucositis ≥ grade 3 or in the event of any grade 4 toxicity apart from neutropenia. Growth factors were not allowed.

Dexamethasone (8 mg) was given as premedication the night before chemotherapy and 1 h before docetaxel infusion. A third dose was also given on the night of chemotherapy. Antiemetic treatment was administered as ondansetron 8 mg or granisetron 3 mg IV pre-chemotherapy.

Assessments

Clinical response was assessed by physical examination after two cycles of docetaxel treatment and classified according to World Health Organization criteria[22] .. A mammogram, ultrasound and MRI were also performed at the end of treatment, before definitive surgery. The surgical procedure was carried out at the discretion of the surgeons (mastectomy or conservative surgery with full axillary dissection). Sentinel lymph node procedure was not considered. All patients who underwent breast surgery received standard radiotherapy in the remaining breast. pCR was defined as no evidence of invasive malignancy in the breast and lymph nodes at the time of definitive surgery. The presence of carcinoma *in situ* was included in this description.

Safety of treatment was monitored by assessment of all adverse events and weekly measurement of hematological and biochemical parameters. Adverse events were graded according to National Cancer Institute common toxicity criteria [23].

Laboratory Methods

Tumor biopsy was performed in all eligible patients before treatment. Histological samples were preferred to facilitate assessment of molecular markers. Paraffin-embedded tumor specimens were examined for the c-*erb*B2 receptor, ER and PR. Estrogen receptors and progesteron receptors were measured using a mononuclear antibody. Tumors were classified as ER or PR negative if <5% of tumor cell nuclei stained positive. Expression levels of the c-*erb*B2 receptor were analyzed by immunochemistry. Samples were scored as follows: score 0, membrane staining in ≤10% of tumor cells; score 1+, partial and/or faint membrane staining in >10% of tumor cells; score 2+, weak to moderate, complete membrane staining in >10% tumor cells; and score 3+, strong, complete membrane staining in >10% of tumor cells. Scores 0 and 1+ were considered negative, and scores 2+ and 3+ were considered positive for c-*erb*B2 overexpression.

Statistical Analysis

The sample size was calculated using with a type I error of 5% and a study power of 80%. The target enrollment was estimated to be 40 patients. All patients who fulfilled the inclusion criteria and received at least one infusion were evaluated for efficacy and safety on an intention-to-treat analysis. The statistical analysis was performed by SPSS version 17. All variables were analyzed by descriptive methods. Chi square test was used to assess the relation between response to Docetaxel (clinical and pathological response) with Her 2 neu expression and Hormonal receptors status.

Results

Patients

- Forty patients were included in the trial. Characteristics of the patients are summarized in Table 1. All patients were evaluated for efficacy and safety on an intention-to-treat basis. Two patients were withdrawn with progressive disease during treatment.

Efficacy

Response rates is illustrated in table 2 .Before treatment, only 20 (50%) patients were eligible for lumpectomy, and no patient initially scheduled for lumpectomy subsequently required mastectomy. The precise surgical procedure carried out was decided upon by the surgeon on a case-by-case basis, with consent from the patient. A pCR, with no evidence of invasive tumor in breast and lymph nodes, was confirmed in 10 of 40 patients (25%), including 2 patients with residual carcinoma *in situ* only.

Immunohistochemistry

Tumor paraffin blocks were obtained from 40 patients before treatment. No correlation was seen between clinical or pathological response with the expression of any of the biological markers assessed, however, the majority of the pCRs were observed in patients with c-*erb*B2-negative tumors. (Table 3)

Safety

Toxicity was assessed in 40 patients (Table 4).

Discussion

In this study the overall response rate was slightly low (65%) compared with other recent studies , the pCR rate was very high with 10 patients (25%) showing no evidence of invasive tumor at definitive surgery.

Most of the neoadjuvant trials reported to date with docetaxel are Phase II studies in combination with an anthracycline and no particular combination or regimen appears to be outstanding in terms of pathological and clinical response rates. Trial B-27 from the National Surgical Adjuvant Breast and Bowel Project (NSABP) demonstrated that the addition of four cycles of sequential, preoperative docetaxel to preoperative AC(Adriamycin /cyclophosphamide) chemotherapy in 2411 patients produced a significantly superior outcome (Overall response rate (ORR)=90.7% ,pCR=26.3%). relative to four cycles of AC alone (ORR=85.7% ,pCR=12.9%). [24].

Some have criticized the design of the NSABP B-27 trial because the preoperative regimens were of different durations (four versus eight cycles) and suggested that the favorable results in the AC/docetaxel arm may be due to the delivery of additional cycles of chemotherapy rather than a distinct taxane benefit. However, the results of a study conducted at the University of Aberdeen, in which eight cycles of neoadjuvant CVAP (cyclophosphamide/vincristine/doxorubicin/prednisolone) chemotherapy were compared with four cycles of CVAP followed by four cycles of docetaxel (eight cycles total) prior to surgery , suggested that the addition of the taxane is indeed beneficial (ORR=66% vs 94% ,pCR= 16% vs 34% respectively). [25]. In that trial, 162 patients with large or locally advanced breast cancer were randomized to the study regimens, and 145 patients completed eight cycles of neoadjuvant therapy.. The results were statistically significant in the primary analysis and in the intent-to-treat population. Furthermore, two patients who received eight cycles of CVAP developed progressive disease after initially responding to the first four cycles of CVAP, which suggests the development of acquired resistance to the regimen. This observation was not seen in the docetaxel group, and this finding supports the use of non-cross-resistant chemotherapy combinations such as anthracyclines plus taxanes.

The NSABP B-27 data are corroborated by the results of the GEPARDUO trial conducted by the German Adjuvant Breast Cancer Group, which compared four cycles of dose-dense AT (doxorubicin/docetaxel) given concomitantly with a sequential regimen of four cycles of doxorubicin/cyclophosphamide followed by four cycles of docetaxel (AC-T) as neoadjuvant therapy in 913 patients with operable breast carcinoma [26]. In the primary analysis, AC-T was associated with a superior pCR rate and ORR, as well as a greater rate of breast-conserving surgery and higher incidence of pathologically negative axillary lymph nodes (ORR=77.2% vs 86.8% ,pCR= 11.5% vs.22.4% respectively).

Conversely, interim results of a phase III trial conducted by the Anglo-Celtic Cooperative Oncology Group showed that there was no benefit to using a concomitant docetaxel/doxorubicin regimen every 3 weeks, relative to AC, in the neoadjuvant setting [27]. A total of 363 women with locally advanced breast cancer were randomized in that trial. At the time of analysis, there was a trend toward a higher ORR with AT (72% versus 62%; $p = 0.07$), but there were no differences in rates of pCR, axillary lymph node involvement, relapse-free survival, or overall survival.

In our study, using single-agent docetaxel in a weekly schedule, resulted in a high number of pathological responses and a favorable toxicity profile. The fact that the proportion of stage II patients included was high (85%), with a relatively small median tumor size (4.6 cm), may have favorably affected this pCR.

Docetaxel was generally well tolerated. Apart from alopecia, asthenia was the most frequent side effect but did not result in patient withdrawal from the study. Nail disorders and acral erythema were frequent, although the number of patients with grade 3–4 events was low, and the symptoms were reversible. Grade 3–4 myelosuppression was rare in our study, with only 2 cases of neutropenia and none of thrombocytopenia.

In neoadjuvant trials, HER-2 **positive** was associated with an improved response to dose-dense paclitaxel in 15 of 21 stage T2–3 BC patients; clinical response was more than double in patients with HER2-positive tumors treated with paclitaxel ($P < 0.05$). Although this trial was prospective, it was not randomized, had a small number of patients and has been published only as an abstract [28]. Another small prospective study failed to demonstrate any correlation between HER-2 positivity and pathological complete response (pCR) in 29 patients with locally advanced breast cancer (LABC), T3 or T4, treated with doxorubicin followed by paclitaxel or paclitaxel followed by doxorubicin in a dose-dense regimen [29]. These negative results were also confirmed using FISH (Her-2/CEP17 >2) in 71 patients treated with neoadjuvant paclitaxel or docetaxel given every 3 weeks [30]. Estévez et al. [31] also failed to demonstrate correlation between pathological or clinical response and HER-2 expression ($P = 0.355$ and $P = 0.942$, respectively) in 56 stage II–III breast cancer patients treated with weekly neoadjuvant docetaxel (ORR 68% and pCR 16%). However, all these three trials were non-randomized, had few patients and in two studies, HER-2 status was not confirmed by FISH.

Interesting findings from Modi et al. [32] showed that phosphorylated-activated HER-2 is associated with clinical resistance to taxanes in 126 patients enrolled in different trials with single-agent taxanes for metastatic and, perhaps, functional assessment of HER-2 status may provide unique predictive information not seen with conventional assessment.

More recently, gene expression profiling techniques have been used for the development of a prediction model for response to docetaxel and paclitaxel.

Chang et al. [33] have reported 92 genes that correlated with docetaxel response ($P = 0.001$) using microarray technology. Sensitive tumors had higher expression of genes involved in cell cycle, cytoskeleton, adhesion, protein transport, protein modification, transcription and stress or apoptosis; whereas resistant tumors showed increased expression of some transcriptional and signal transduction genes. However, this study was not designed to discover specific genes for docetaxel response or resistance, but rather to identify patterns of many genes that could be used as a predictive test in patients with breast cancer. [34]. Ayers et al. [35] have examined the feasibility of developing a multigene predictor of pCR to sequential weekly paclitaxel and FAC (T/FAC) neoadjuvant CT for breast cancer. pCR was achieved in 13 patients (31%) out of 42 patients: 24 patients were used in the training set and 18 patients in the validation set. The authors could not identify any single marker that was sufficiently associated with pCR to be used as an individual predictor. [36].

In our study, we found no association between overexpression of c-*erb*B2 and the clinical and pathological response to neoadjuvant docetaxel. However, the majority of the pCRs were observed in patients with c-*erb*B2-negative tumors. The number of the patients in our study was low, and this trend should be studied in a larger trial. In addition, these data suggest that blocking c-*erb*B2 overexpression using a monoclonal antibody such as trastuzumab (Herceptin) could enhance the response to docetaxel.

This pilot phase II trial highlights the need to identify the best schedule for neoadjuvant docetaxel. In our study, single-agent docetaxel given on a weekly schedule appeared to be very effective and well tolerated as neoadjuvant chemotherapy, with a high documented pCR.

Because at present there is no evidence that primary systemic therapy offers a disease-free survival or overall survival benefit over adjuvant systemic therapy, knowledgeable patients may choose to receive systemic therapy before surgical resection to take advantage of the response-assessment of the primary tumor before it is removed.

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Tables

Table 1. Baseline characteristics of patients

	No. of patients (%)
Total no. of patients	40 (100)
Age (yr)	
Mean	53±SD19.7
Range	28–73
Tumor size (cm)	
Mean	4.4±SD1.7
Range	2–8.5
ECOG[a] performance status	
0	39 (97.5)
1	1 (2.5)
Menopausal status	
Premenopausal	18 (45)
Perimenopausal	2 (5)
Postmenopausal	20 (50)
Disease stage	
IIA	16 (40)
T2N0M0	16 (40)
IIB	18 (45)
T3N0M0	14 (35)
T2N1M0	4 (10)
IIIA	4 (10)
T2N2M0	2 (5)
T3N1M0	2 (5)
IIIB	2 (5)
T3N2M0	2 (5)

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Table 2: Response rate to docetaxel on intention-to-treat basis

	No. of patients	%
CR	10	25
Partial response	16	40
Stable disease	12	30
Progressive disease	2	5
Response rate (95% confidence interval)	26	65 (56–80)

Table 3 : Relation between biological markers and Response

	Her 2 neu positive	Her 2 neu negative	
Pathological CR	2	4	6
Non Pathological CR	15	19	34
Total	17	23	40
P value 0.6 (Non Significant)			
	Estrogen Receptor positive	**Estrogen Receptor negative**	
Pathological CR	3	3	6
Non Pathological CR	23	11	34
Total	26	14	40
P value 0.4 (Non Significant)			
	Her 2 neu positive	**Her 2 neu negative**	
Clinical Response	12	14	26
Non responders	5	9	14
Total	17	23	40
P value 0.52 (Non Significant)			
	Estrogen Receptor positive	**Estrogen Receptor negative**	
Clinical Response	15	11	26
Non responders	9	3	16
Total	26	14	40
P value 0.33 (Non Significant)			

Table 4. Hematological and nonhematological adverse events (*n* = 40)

Adverse event	Grade 1 or 2 No. of patients	(%)	Grade 3 or 4 No. of patients	(%)
Hematological				
Anemia	2	(5)	1	(2.5)
Leucopenia	20	(50)	0	
Neutropenia	20	(50)	2	(5)
Thrombocytopenia	4	(10)	0	
Nonhematological				
Alopecia	40	(100)		
Anxiety	0		1	(2.5)
Asthenia	24	(60)	8	(20)
Conjunctivitis	10	(25)	2	(5)
Cutaneous	20	(50)	6	(15)
Diarrhea	16	(40)	2	(5)
Hypersensitivity	4	(10)	0	
Infection	6	(15)	1	(2.5)
Nail disorder	22	(55)	7	(17.5)
Nausea/Vomiting	16	(40)	0	
Paresthesia	21	(42.5)	2	(5)
Peripheral edema	9	(22.5)	0	
Stomatitis	14	(35)	2	(5)