A Phase I Study of Docetaxel Plus Cyclophosphamide in Solid Tumors followed by a Phase II Study as First-Line Therapy in Metastatic Breast Cancer[1]

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ABSTRACT

Purpose: **In Phase I, the purpose was to determine the maximum tolerated dose and pharmacokinetics of docetaxel plus cyclophosphamide (DC) with and without granulocyte colony-stimulating factor in the treatment of patients with solid tumors. For Phase II, the purpose was to determine the safety and efficacy of this combination as first-line treatment in patients with metastatic breast cancer (MBC).**

Experimental Design: **In Phase I (45 patients), docetaxel was escalated from 60 mg/m^2 to 85 mg/m^2, and cyclophosphamide from 600 mg/m^2 to 800 mg/m^2. Pharmacokinetic evaluation of docetaxel was performed in 19 patients with MBC. In Phase II (34 patients), patients received cyclophosphamide (600 mg/m^2) followed by docetaxel (75 mg/m^2), i.v.**

Results: **In Phase I, the dose-limiting toxicity was neutropenia-related events. The maximum tolerated dose for DC was 75 mg/m^2/700 mg/m^2 in solid tumor patients treated previously and 75 mg/m^2/800 mg/m^2 for patients not treated previously for MBC. Dose escalation of docetaxel >75 mg/m^2 was not tolerated, despite prophylactic granulocyte colony-stimulating factor treatment. In Phase II, 71% of patients received prior anthracycline therapy. Neutropenic fever requiring i.v. antibiotics occurred in 6 patients (19%). One patient had grade 3 neuropathy. There was no cardiotoxicity. The overall Phase II intent-to-treat objective response rate was 65% (complete responses, 12%). The median overall survival was 22 months, and the median time to progression was 6 months.**

Conclusions: **DC combination therapy is an active regimen with acceptable toxicity and is appropriate regardless of prior anthracycline therapy. In view of the high activity and lack of cardiotoxicity, this combination warrants additional investigation in early stage breast cancer and in combination with trastuzumab.**

INTRODUCTION

Breast cancer is the most common malignancy of American women. This year, an estimated 192,200 new cases will be diagnosed, and 40,800 women will die of the disease, making breast cancer second only to lung cancer as the cause of cancer death in women in the United States (1). Anthracycline-containing regimens, such as 5-fluorouracil, doxorubicin, and cyclophosphamide, 5-fluorouracil, epirubicin, and cyclophosphamide, or doxorubicin plus cyclophosphamide, are the most frequently used combination regimens for MBC[3] (2, 3) In recent years, many patients with early high-risk breast cancer received anthracycline-containing adjuvant or neoadjuvant regimens. Although doxorubicin is considered the most important component of combination chemotherapy in MBC, some patients cannot tolerate its toxicities, choose not to accept the safety profile, or have previous anthracycline exposure. Furthermore, few regimens are effective in patients with anthracycline-exposed or anthracycline-resistant breast cancer (4–8). Therefore, an effective regimen that does not contain an anthracycline must be identified.

Docetaxel is a well-tolerated agent that has significant activity against breast cancer (9, 10). Initial Phase II studies in MBC patients treated previously, found response rates to range from 18 to 58% (4, 6, 11). Phase III randomized trials of docetaxel in >1000 patients have found response rates ranging from 30 to 48%, establishing its activity as a single agent in patients with MBC (8, 12, 13).

Although not supported by data from prospective, randomized trials, there is some suggestion that docetaxel in combination with an anthracycline may be a more active regimen than docetaxel alone. Docetaxel plus doxorubicin, docetaxel plus

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[3] The abbreviations used are: MBC, metastatic breast cancer; MTD, maximum tolerated dose; G-CSF, granulocyte colony-stimulating factor; CBC, complete blood count; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTP, time to progression; OS, overall survival; CL, clearance rate; PK, pharmacokinetics.

doxorubicin plus cyclophosphamide, and docetaxel plus epirubicin have shown objective response rates of 60%, 55%, and 62.5%, respectively. Moreover, docetaxel in combination with nonanthracyclines appears to have superior activity to docetaxel monotherapy. A Phase III trial found that docetaxel monotherapy resulted in an overall response rate of 30% and median OS of 11.5 months, whereas the combination of docetaxel plus capecitabine resulted in an overall response rate of 42% and median OS of 14.5 months (14).

Used as a single agent in patients with MBC, cyclophosphamide produces an objective response rate of 34% (15). Cyclophosphamide is an integral constituent of most established first-line combination chemotherapy regimens for the management of all stages of breast cancer (2, 3).

The combination of DC chemotherapy exhibited efficacy in preclinical tests (16). Moreover, combining the two drugs allowed >60% of the full single-agent dose of each drug to be used safely (16). Clinical studies have shown that taxanes combined with alkylating agents are effective in treating MBC and other solid tumors (17–20). Phase I studies of paclitaxel combined with cyclophosphamide have shown safety (18) and overall response rates of 25% for patients with MBC treated previously, and 50% for those with untreated MBC (20).

The primary goals of the current study were to develop a combination regimen that was both safe and well-tolerated in women with MBC who were not eligible for anthracyclines, or who could not tolerate the toxicity of anthracyclines. Docetaxel and cyclophosphamide were chosen in view of their activity as single agents, their activity in combination, and the extent of experience with these two agents in the treatment of breast cancer. It is serendipitous that this regimen lacks cardiotoxicity and makes for an appealing combination with trastuzamab.

Thus, we determined the MTDs of DC when used in combination in patients with previously treated or untreated solid tumors. We also determined the MTD of this combination without and with G-CSF in patients with untreated MBC (no prior chemotherapy for metastatic disease). Pharmacokinetic evaluation of docetaxel was performed in patients with MBC. We then conducted a prospective Phase II study to assess the efficacy and safety of the combination of DC combination as a first-line therapy in patients with MBC.

PATIENTS AND METHODS

Study Design and Patients. Patients in Phase I were divided into three cohorts: (*a*) cohort A was composed of 18 patients with solid tumors who were allowed previous treatment for metastatic cancer; (*b*) cohort B included 18 patients not treated previously for MBC; and (*c*) cohort C consisted of 9 patients with untreated MBC who received G-CSF (filgrastim, Neupogen; Amgen Corp.) after chemotherapy until the WBC count was >10,000/μl.

Patients with histologically confirmed solid tumors were eligible for Phase I, cohort A. These patients were eligible regardless of the number of prior regimens of chemotherapy, hormonal therapy, radiotherapy, or biological therapy, provided they had not received these or investigational agents within 4 weeks of study entry.

Patients with histologically confirmed adenocarcinoma of the breast with progressive metastatic disease were considered for both Phase I and Phase II. These patients were deemed ineligible for cohort B or C of the Phase I study and for the Phase II study if they had received prior chemotherapy for MBC.

Patients were eligible for inclusion if they had recovered from reversible toxicity caused by prior therapy, had a survival expectancy of >12 weeks, had a performance status of >60% on the Karnofsky scale (21), and had normal function of the bone marrow (absolute granulocyte count >2,000/μl, platelet count >100,000/μl), liver (serum total bilirubin less than the institutional upper limit of normal and alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase <1.5 times the upper limit of normal), and kidneys (serum creatinine <2.0 mg/dl or creatinine clearance >60 ml/min).

All of the patients may have had prior adjuvant or neoadjuvant chemotherapy, provided that they had not received taxane-containing regimens.

Patients were also excluded if they had meningeal or brain metastasis, symptomatic peripheral neuropathy (National Cancer Institute grade >1), or other serious medical or psychiatric illness. Before treatment, all of the patients were advised of the investigational nature of this study and signed a written informed consent form approved by The University of Texas M. D. Anderson Cancer Center Surveillance Committee (Institutional Review Board).

Pretreatment and Follow-Up Evaluation. Baseline evaluation consisted of: (*a*) a complete medical history and physical examination; (*b*) a CBC; (*c*) measurement of prothrombin time and partial thromboplastin time; (*d*) serum biochemical profile (SMA-20); (*e*) an electrocardiogram; (*f*) a urinalysis; (*g*) a chest radiograph; (*h*) an abdominal computed tomography scan; and (*i*) measurement of urine or serum chorionic gonadotropin in patients with childbearing potential. Patients had other appropriate imaging studies, as clinically indicated, to document the extent of disease. All of the patients had vital signs performed every 15 min during administration and 2 h after administration. Between treatments, patients had a CBC twice weekly during the first two courses and then weekly along with a serum biochemical profile. Before each treatment, the patients had a CBC, SMA-20, prothrombin time and partial thromboplastin time, urinalysis, electrocardiogram, physical examination, tumor measurements, and toxicity profile assessment. Appropriate imaging studies to assess objective response were performed after every two cycles of treatment.

Treatment Plan. Cyclophosphamide (Cytoxan; Bristol-Myers-Squibb Pharmaceuticals, Princeton, NJ, or Neosar; Adria Laboratories, Columbus, OH) then docetaxel (Aventis Pharmaceuticals, Bridgewater, NJ) were sequentially administered i.v. over 1 h. At the onset of the study, premedication consisted of dexamethasone 8 mg administered p.o. twice a day for 5 days, starting 24 h before docetaxel administration. On April 18, 1997, the premedication dexamethasone administration was amended to a duration of 3 days. For the Phase I study, the starting dose of docetaxel was 60 mg/m^2, and the starting dose of cyclophosphamide was 600 mg/m^2. The doses of both agents were escalated sequentially and an MTD established in each cohort of patients as described below. For patients experiencing unacceptable toxicity (grade >3 nonhematologic toxicity, grade

4 neutropenia for >7 days, grade 4 neutropenia with fever or infection, grade >3 neutropenia at day 22, and temperature >38°C requiring i.v. antibiotics), the dose of docetaxel and cyclophosphamide were each reduced by 25%. For patients experiencing peripheral neuropathy or cutaneous reactions as the only toxicity, only the docetaxel was reduced by 25%. A maximum of two dose reductions were allowed per patient. Administration of both agents was repeated every 21 days until disease progression was documented or until toxic effects precluded additional therapy.

After the MTD was identified in patients with solid tumors and patients with untreated MBC, the MTDs of these agents with G-CSF were determined in a third cohort comprised of patients with untreated MBC (Phase I, cohort C). G-CSF was given in a single daily dose of 5 μg/kg to 9 patients on days 2–8 of each course or until WBC >10,000 cells/μl. Patients entering the Phase II study received cyclophosphamide 600 mg/m^2 and docetaxel 75 mg/m^2 by the same schedule of administration and dose reductions used in Phase I.

Assessment of Toxicity. Toxic effects were graded by the National Cancer Institute Common Toxicity Criteria. Other toxic effects were graded as mild (asymptomatic or minor symptoms that did not require treatment), moderate (symptoms that required minor treatment), or severe (symptoms that interfered with function and that required major treatment). Neutropenic fever was nongraded and was defined as a temperature >38.5°C in a patient with an absolute granulocyte count <500/mm^3.

Assessment of Response. Assessment of antitumor activity was evaluated after every two courses. Objective responses were graded according to standard criteria (22) for CR, PR, SD, or no change, and PD. Tumor response was based on two assessments performed at least 6 weeks apart. The TTP was calculated from the time of the first dose of DC to the time of the first objective evidence of tumor progression. OS was calculated from the time of patient enrollment in the study to the time of documented death. For patients who were alive or who were lost to follow-up, end points were based on the date they were last known to be alive or the date of last available information.

Pharmacologic Studies. Analysis of blood plasma concentrations of docetaxel was performed during the first cycle of therapy in the first 19 patients in the Phase I study. Blood samples were collected before the infusion of docetaxel began and again 30 min into the 1-h infusion, and 2, 4, 6, and 24 h after completion of the infusion. The systemic CL, concentration at steady state, and plasma half-life for docetaxel were calculated using the method described by Bruno *et al.* (23) and Vergniol et al. (24).

The collected data permitted elaboration and validation of a population PK model that was used to estimate the PK parameters of each individual based on plasma concentrations, using Bayesian methods.

The PK model is a three-compartment structural model with first-order elimination. The interpatient and residual variability of PK parameters is modeled as described previously (23, 25). Individual plasma clearance, area under the plasma concentration-time curve, peak plasma level, and time at which plasma levels exceeded given threshold levels were used as measures of drug exposure.

Table 1 Phase I: characteristics of patients with solid tumors at study entry

Characteristic	Value
Total patients	45
No. of patients with breast cancer	32
Median age (range), years	53 (29–73)
Median Karnofsky performance status (range), %	90 (60–100)
No. of patients with prior hormonal therapy (%)	13 (29%)
No. of patients with prior chemotherapy (%)	39 (87%)
No. of patients with prior anthracycline therapy (%)	29 (64%)
Median no. of metastatic sites (range)	2 (1–5)

Statistical Considerations. A main objective of the Phase I study was to establish the dose at which the combination of DC was to be used in the Phase II portion of the study. Doses were escalated in groups of 3 patients until unacceptable toxicity was observed (grade >3 nonhematologic toxicity, grade 4 neutropenia for >7 days, grade 4 neutropenia with fever or infection, grade >3 neutropenia at day 22, and temperature >38°C requiring i.v. antibiotics). If unacceptable toxicity occurred in 1 or 2 of 3 patients, then 3 additional patients were accrued at that level. MTD was reached when ≥3 patients in a group experienced unacceptable toxicity. Determining whether G-CSF would allow additional dose escalation required an additional 9 patients.

To calculate sample size for the Phase II study, we made the assumption that an objective response rate >70% was considered sufficiently active to warrant additional testing of this combination. At least 31 patients would be required to detect an objective response rate >70% (with a power of 90%), although we enrolled a total of 34 patients.

The safety, efficacy, laboratory, and adverse event data were reviewed to ensure that evaluability and responses had been determined appropriately. Patients who died during therapy or who were lost to follow-up were considered to have PD as of the date of death or last follow-up date unless a definite clinical or autopsy diagnosis indicated drug-related death or death because of causes unrelated to therapy or disease.

The percentage of patients attaining a CR and the percentage of patients attaining either a CR or a PR were estimated, and 95% two-sided confidence intervals were calculated. The survival distributions for OS and TTP were estimated using the Kaplan-Meier (product-limit) method. Patients for whom the endpoints for these analyses (*i.e.*, SD, still alive as of last follow-up) were unavailable and were censored using the most recent available data.

RESULTS

Patient Characteristics. Seventy-nine patients were enrolled in this Phase I/II study between August 27, 1994, and April 2, 1999: 45 in the Phase I study and 34 in the subsequent Phase II study. All of the patients included in the trial were evaluated according to intent-to-treat analysis, including 1 who died during the course of treatment. Reported results were accurate as of April 10, 2001. The characteristics of the patients treated in the Phase I study are listed in Table 1, and those in the Phase II study are listed in Table 2. Of the 45 patients in the Phase I study, 38 were women and 7 were men; 32 had MBC,

Table 2 Phase II: characteristics of patients with MBC at study entry

Characteristic	Value
Total patients	34
Median age (range), years	55 (39–76)
Median Karnofsky performance status (range), %	90 (60–100)
No. of patients with prior hormonal therapy	14 (41%)
No. of patients with prior chemotherapy	27 (79%)
No. of patients with prior anthracycline therapy	24 (71%)
Median no. of metastatic sites (range)	2 (1–6)
No. of patients ER+/PR+[a]	10 (29%)
No. of patients ER+/PR−	3 (9%)
No. of patients ER−/PR+	2 (6%)
No. of patients ER−/PR−	17 (50%)
No. of patients ER/PR unknown	2 (6%)
No. of patients Her-2/*neu* positive	3 (15%)
No. of patients Her-2/*neu* negative	17 (50%)
No. of patients Her-2/*neu* unknown	14 (35%)

[a] ER, estrogen receptor; PR, progesterone receptor.

6 had sarcoma, 3 had colon cancer, and 4 had other solid tumors. In general, patients had a good Karnofsky performance status and more than one site of metastasis. Most patients in the Phase I study had prior chemotherapy, and 29 patients had received a previous adjuvant or preoperative regimen containing an anthracycline.

The median age of the 34 patients in the Phase II study was 55 years (range, 39–76 years). Phase II patients had a good Karnofsky performance status and two or more metastatic sites. Thirteen patients were positive for the estrogen receptor, 19 patients were negative for the estrogen receptor, and the remaining 2 patients had no data available on estrogen receptor testing. Only 20 patients had measurement of HER-2/*neu* by immunohistochemistry or by fluorescent *in situ* hybridization testing. From the patients tested for HER-2/*neu*, 3 patients were HER-2/*neu* positive, and 17 were HER-2/*neu* negative. Most patients had received prior chemotherapy. Seventy-one percent in the Phase II study had received an anthracycline, and 79% had received cyclophosphamide as a previous preoperative or postoperative regimen. No patients in the Phase II study received trastuzumab.

Phase I Safety Profile. In Phase I, a total of 45 patients received a total of 236 courses of DC. The numbers of patients, the dose escalation scheme, and the first cycle hematologic toxicities are shown in Table 3. The median number of cycles was 5 (range, 1–17 cycles). Nonhematologic toxicities are shown in Table 4.

Neutropenia complicated by fever was seen in 23 patients (51%) during any cycle. Febrile neutropenia requiring admission for i.v. antibiotics occurred in 14 patients (9 patients received oral antibiotics). Nine patients had two or more episodes of neutropenic fever. Twelve patients had febrile neutropenia with a documented infection. One patient died of nonneutropenic sepsis after admission to an outside hospital for nausea, vomiting, and abdominal pain.

The most common grade 3 or 4 nonhematologic toxicities were fatigue and myalgia. Alopecia was total and universal in most patients. Three patients each experienced one grade 2 hypersensitivity reaction. Stomatitis was frequent (34 patients, 76%, grade 1 and 2) but rarely severe (only 2 patients with grade 3 or 4). Noninfectious conjunctivitis was occasionally seen, and was described as excessive tearing and occasional ocular itching. Thirty-one patients (69%) developed a grade 1 or 2 peripheral neuropathy that was predominantly of a sensory type and nondisabling. The patients experienced mild paresthesia or dysesthesia in the fingertips or toes or both.

Three patient cohorts were evaluated for MTD in this study (Table 3). The MTD for cohort A was 75 mg/m^2 docetaxel and 700 mg/m^2 cyclophosphamide. The MTD for cohort B was 75 mg/m^2 docetaxel and 800 mg/m^2 cyclophosphamide. The use of G-CSF did not allow dose escalation, and the MTD for cohort C remained at 75 mg/m^2 docetaxel and 800 mg/m^2 cyclophosphamide. There is little evidence to support the efficacy of cyclophosphamide at doses >600 mg/m^2 in patients with breast cancer (26–28). Therefore, we chose a lower dose of cyclophosphamide (600 mg/m^2 rather than 800 mg/m^2) to decrease the likelihood of neutropenia-related events and reducing the dose of docetaxel. Thus, 75 mg/m^2 docetaxel in combination with 600 mg/m^2 cyclophosphamide was the recommended Phase II regimen for patients not treated previously for MBC.

Phase II Safety Profile. In Phase II, 34 patients received a total of 254 courses of the combination of DC: 149 cycles were administered at dose level 0, 88 cycles at dose level −1 (450 mg/m^2 cyclophosphamide and 45 mg/m^2 docetaxel), and 17 cycles at dose level −2 (340 mg/m^2 cyclophosphamide and 35 mg/m^2 docetaxel). There was 1 early death (15 days after first cycle, etiology undetermined), and 1 patient was found to be ineligible (after 1 cycle of therapy). The median number of cycles per patient was 8 (range, 1–17 cycles).

Phase II study toxicities are listed in Table 5. Among the 34 patients treated with 75 mg/m^2 of docetaxel and 600 mg/m^2 of cyclophosphamide, febrile neutropenia was seen in 12 patients (35%); no infection was considered life-threatening, and only 6 of these patients required hospitalization for i.v. antibiotic therapy. Nonfebrile neutropenia occurred in 29 patients (85%). There were no other significant hematologic toxicities. Nonhematologic toxicities were similar to those seen in the Phase I study.

Phase I Response. Three medical oncologists and one radiologist from our institution confirmed all of the responses. Among the 32 patients who had MBC with evaluable disease, in Phase I, 18 (56%) achieved a PR, and 4 (13%) had a CR. The overall objective response rate was 69%, and the median OS duration was 18.3 months. Among patients with other solid tumors, 1 patient (sarcoma) had a brief PR.

Phase II Response Data. The outcomes of Phase II treatment are summarized in Table 6. Among the 34 patients included in the intent-to-treat analysis, objective responses were observed in 22 patients (65%): 18 patients (53%) had a PR and 4 patients (12%) had a CR. SD was observed in 7 patients (21%). The other 5 patients (14%) had PD or withdrew from the study. As seen in Fig. 1, the median OS was 22 months (range, 1 to 39+ months). The median TTP was 6.0 months (range, 0.5 to 39+ months; Fig. 2).

PK Studies. Pharmacokinetic studies were performed in the first 19 patients with previously untreated MBC (cohorts B and C; Table 7) that received a combination of 75–85 mg/m^2 of docetaxel and 700–800 mg/m^2 of cyclophosphamide. These

Table 3 Phase I cohorts and first cycle hematologic toxicity

DC (mg/m^2)	Cohort[a]	Total	DLT[b]	Neutropenia			Anemia grade 3–4	Thrombocytopenia grade 3–4
				Grade 3	Grade 4	NF[c]		
60/600	A	6	1	2	2	0	1	0
75/600	A	3	0	0	3	2	0	0
75/700	A	6	2	1	5	2	0	0
75/800	A	3	3	0	3	2	0	0
75/700	B	3	0	0	3	1	0	0
75/800	B	6	1	0	6	2	0	0
85/800	B	3	3	0	3	2	0	0
80/600	B	6	2	1	5	3	2	0
75/800	C	3	0	1	1	0	0	0
85/800	C	6	3	1	3	3	2	0
Total		45	15	6	34	17	5	0

[a] Phase I cohorts: A, patients treated previously for metastatic solid tumors; B, patients not treated previously for MBC; C, patients not treated previously for MBC who received G-CSF.
[b] DLT, grade 4 nonhematologic toxicity, grade 4 neutropenia lasting $>$ 7 days, grade 4 neutropenia with fever or infection, grade 4 thrombocytopenia.
[c] NF, neutropenic fever.

Table 4 Phase I: number of patients with nonhematologic toxicity during any cycle

Toxicity	National Cancer Institute grade			
	1	2	3	4
Diarrhea	20	8	2	0
Edema	7	11	0	0
Emesis	6	4	0	0
Fatigue	8	18	17	0
Hand foot syndrome	9	2	1	0
Infection	2	7	15	0
Myalgia	13	18	4	0
Nail changes	18	2	0	0
Nausea	13	12	0	0
Sensory change	20	11	0	0
Stomatitis	17	17	2	0

Table 5 Phase II: number of patients with National Cancer Institute common toxicity criteria toxicity during any cycle

Toxicity	National Cancer Institute grade			
	1	2	3	4
Hematologic toxicities				
Anemia	14	14	4	0
Febrile neutropenia (non-graded)	12			
Neutropenia	2	0	2	29
Thrombopenia	6	0	0	0
Nonhematologic toxicities				
Diarrhea	13	10	1	0
Edema	12	4	0	0
Emesis	7	9	0	0
Fatigue	4	13	15	0
Hand foot syndrome	14	3	1	0
Infection	0	7	7	1
Myalgia	6	20	5	0
Nail changes	15	3	0	0
Nausea	7	17	1	0
Sensory change	16	7	1	0
Stomatitis	12	14	1	0

results are presented in Table 7 and show no significant effect of cyclophosphamide on docetaxel PK. This finding was not surprising and confirms published observations (23, 25).

DISCUSSION

This study has shown that the nonanthracycline-containing combination of 75 mg/m^2 of docetaxel plus 600 mg/m^2 of cyclophosphamide is safe and highly effective when given every 21 days. Our intent-to-treat objective response rate was 69% in Phase I and 65% in the Phase II portion; 86% of Phase II patients had a CR, a PR, or SD). Although this response rate is lower than the 70% response rate we estimated in study design, the regimen DC has activity in MBC. The efficacy presented in this paper makes DC an attractive alternative to anthracycline containing regimens. Moreover, there was a 22-month median OS.

The safety and efficacy of DC appear to be superior to the results seen with docetaxel as a single agent in Phase II trials. This conclusion is supported by two Phase II trials of second-line single agent docetaxel in women with MBC. The study by Valero *et al.* (4) found an intent-to-treat objective response rate of 51% (53% in evaluable patients) and a median OS of 13.5 months. In first-line MBC, others have reported intent-to-treat objective response rates of 51–60% with docetaxel monotherapy (29, 30).

Although the current study is a Phase II, single-institution study, our results appear to be superior to the activity of docetaxel monotherapy in three multi-institution, randomized trials that demonstrate response rates of 30–50% in the subset of MBC patients treated in first-line with docetaxel monotherapy (8, 12, 13).

A Phase III randomized trial established the superiority of docetaxel in combination randomized against docetaxel as monotherapy. When docetaxel plus capecitabine was compared with docetaxel alone, O'Shaughnessy *et al.* (14) found improvement in objective response rate (42 *versus* 30%), time to disease progression (6.1 *versus* 4.2 months), and median survival (14.5 *versus* 11.5 months) when docetaxel was given in combination.

Table 6 Response rates for patients treated with docetaxel and cyclophosphamide in Phase II

Response	No. of patients	% of patients (95% confidence interval)
Overall response	22	65 (49–81)
CR	4	12 (1–33)
PR	18	53 (36–70)
SD	7	21 (7–35)
PD	5	14 (2–26)

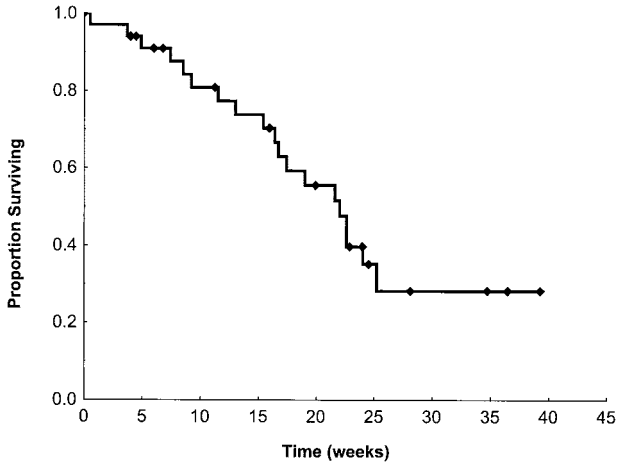

Fig. 1 Kaplan-Meier estimate of the cumulative probability of survival of patients treated with docetaxel in combination with cyclophosphamide (♦, a censored observation; $n = 34$).

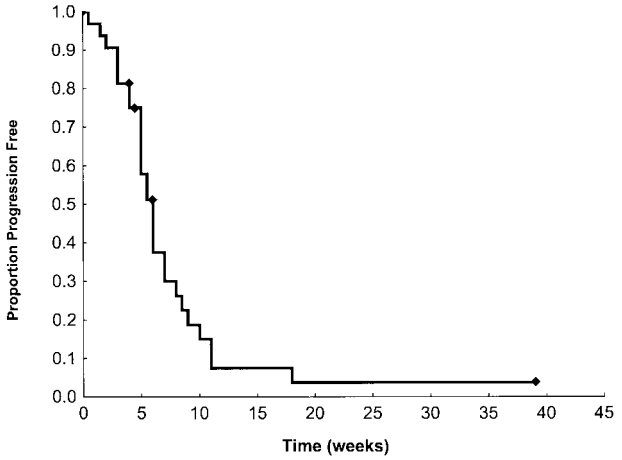

Fig. 2 Kaplan-Meier estimate of the cumulative probability of remaining disease free for patients treated with docetaxel in combination with cyclophosphamide (♦, a censored observation; $n = 34$).

Docetaxel has also been combined with either vinorelbine (31) or epirubicin (32) in the first-line therapy of MBC with objective response rates of 64% and 66%, respectively. Whereas the combination of cisplatinum and docetaxel had a 36% response rate as second-line therapy (33, 34), the first-line response rates were 77% in anthracycline-naive patients (35) and 55% in anthracycline-exposed patients (36) with MBC. The current study of DC indicates that this regimen has comparable activity to other docetaxel containing two-drug combinations.

The TAX 306 trial randomized 429 patients with MBC to receive either doxorubicin plus cyclophosphamide or doxorubicin plus docetaxel. This study reported superior response rates with the AT combination. This trial additionally established docetaxel as an effective agent when given in combination for MBC (37).

Although DC appears comparable in efficacy to other combination regimens containing docetaxel, there are no randomized trials directly comparing DC to a docetaxel-containing triplet. The Phase II combination of docetaxel plus doxorubicin plus cyclophosphamide (Taxotere plus Adriamyclin plus cyclophosphamide) was used in anthracycline-naïve and taxane-naïve patients with MBC with an intent-to-treat objective response rate of 67% and a median TTP of 10.2 months (17, 38). It is interesting to note that our Phase II intent-to-treat objective response rate of 65% is comparable with that of the Taxotere plus Adriamyclin plus cyclophosphamide regimen. Additionally, the current study included patients that had received a prior anthracycline-containing regimen (71% of patients), whereas the patients treated with TAC were anthracycline-naive. There were more estrogen receptor-positive patients in the TAC study (63% *versus* 38%), and fewer patients in the TAC study had prior chemotherapy (31% *versus* 79%). Thus, patient selection may contribute to the longer median TTP with TAC. The TAC regimen has now been studied in Phase III in patients with MBC, <25% of whom have been treated with adjuvant anthracycline therapy (38). This study found that in 484 patients with MBC randomized to either TAC or 5-fluorouracil, doxorubicin, and cyclophosphamide, there was a 55% (range, 49–61%) overall response rate and a median OS of 21 months (range, 17–25 months) for patients receiving TAC. Thus, it appears that the efficacy of TAC from Phase I and Phase II studies is similar to DC, as presented in the current study.

A current Phase III, prospective, randomized trial is comparing postoperative doxorubicin plus cyclophosphamide to DC (termed TC) in patients with stage I-III operable, invasive breast cancer (39). The preliminary results suggest that the combination of DC is well-tolerated. If this trend continues as the study matures, DC may be another option in the treatment of patients with high risk, early stage breast cancer.

In our study, the combination of 75 mg/m^2 docetaxel and 600 mg/m^2 cyclophosphamide was well tolerated in both the Phase I and the Phase II portions of this study. The Phase I dose-limiting toxicity was neutropenic fever or neutropenia-related infection. There appears to be similar grade 3/4 neutropenic fevers or infections in the current Phase I dose escalation study (51% neutropenic fever, 91% neutropenia, and 33% infection in patients during any cycle) compared with other studies using docetaxel alone. This Phase I, dose escalation toxicity profile was obtained in patients receiving up to 85 mg/m^2 docetaxel and 800 mg/m^2 cyclophosphamide.

The Phase II portion of our study found neutropenic fever in 38% (grade 4 neutropenia with grade >1 fever), neutropenia in 97%, and infection in 25% of patients during any cycle. In comparison, a Phase II study of single agent docetaxel (100

Table 7 Pharmacokinetic parameters of docetaxel in patients treated with docetaxel plus cyclophosphamide

D (mg/m^2)[a]	C (mg/m^2)	Total patients	BSA (m^2 ± SD)	C_{max} (μg/ml ± SD)	AUC (μg*h/m ± SD)	CL (liter/h/m^2 ± SD)	V_{ss} (liter/m^2 ± SD)	$T_{1/2}$ (h ± SD)
700	75	7	1.67 ± .05	1.82 ± .43	2.87 ± .24	26.3 ± 2.2	219 ± 299	14.2 ± 16.8
600	80	6	1.86 ± .16	2.03 ± .27	3.31 ± .72	25.0 ± 5.7	219 ± 97	19.9 ± 7.2
800	85	6	1.88 ± .24	1.68 ± .73	3.10 ± .69	28.6 ± 6.2	240 ± 336	11.8 ± 11.3

[a] C, cyclophosphamide; D, docetaxel; BSA, body surface area; C_{max}, maximum concentration; AUC, area under the concentration-time curve, V_{ss}, volume at steady state; $T_{1/2}$, terminal half-life.

mg/m^2) in patients treated previously for MBC at our institution reported neutropenic fever (grade 4 neutropenia with grade >1 fever) in 51%, neutropenia in 96%, and grade 3 or greater infection in 26% of patients during any cycle (4). A second Phase II study of docetaxel at 100 mg/m^2 reported neutropenic fever requiring i.v. antibiotics in 33% of patients and neutropenia in 95% of patients (6). Neutropenia in Phase III trials of docetaxel monotherapy (100 mg/m^2) was reported from 93 to 94% (8, 13). These trials also reported 5.7–9% rates of grade 4 neutropenia with grade >2 fever during any cycle of docetaxel. These results suggest that there is no increase in toxicity when the docetaxel dose is reduced from 100 mg/m^2 to 75 mg/m^2 and combined with cyclophosphamide. The incidence of skin rash, hypersensitivity reactions, fatigue, myalgia, and fluid retention were similar to those reported previously in patients receiving 75 mg/m^2 of docetaxel (4, 11, 39).

One aspect of this study was to determine whether dose escalation was possible with the addition of prophylactic G-CSF in patients with untreated MBC. Since the initial design of this study in 1994, it has become apparent that high-dose chemotherapy and prophylactic G-CSF in the MBC setting are of unproven benefit (40–44). Thus, it is not surprising that the MTD was similar without or with G-CSF for patients treated previously with MBC. This is the rationale why G-CSF was not required in the Phase II study.

The maximum concentration in micrograms per milliliter and area under the curve in microgram + hours per minute values for docetaxel in this study are concordant with the pharmacokinetic profile of docetaxel administered as a single agent. The total plasma CL of 27 liter/h/m^2 (SD = 6 liter/h/m^2) in this study was relatively stable over the cyclophosphamide dose range and was similar to that observed for docetaxel administered alone (22 liter/h/m^2, SD = 11 liter/h/m^2; Ref. 23).

The rationale underlying the activity and future potential of this combination is appealing. Each agent works via a different mechanism of action with a nonoverlapping nonhematologic toxicity profile. Moreover, preclinical studies have shown that there is limited cross-resistance and additive antitumor activity when these two agents are combined (16, 45). In patients with anthracycline-resistant MBC or those who are unable to tolerate the toxicity of anthracyclines, the combination of DC is an effective and well-tolerated first-line treatment for MBC. This study has laid the groundwork for a Phase III trial comparing the safety and activity of postoperative DC in the setting of early stage breast cancer.

Cardiotoxicity is a critical limiting toxicity with anthracycline-containing regimens and precludes their combination with trastuzumab (Herceptin). Because the combination of DC has minimal cardiotoxicity, future studies may be directed at combining the promising activity of this regimen with trastuzumab in the treatment of patients with Her-2/*neu* growth factor receptor-expressing tumors.

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A Phase I Study of Docetaxel Plus Cyclophosphamide in Solid Tumors followed by a Phase II Study as First-Line Therapy in Metastatic Breast Cancer

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