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Published on: 01 Aug 1999 - Journal of Clinical Oncology (American Society of Clinical Oncology)

Topics: Docetaxel, Chemotherapy, Epirubicin, Mitoxantrone and Metastatic breast cancer

Prospective Randomized Trial of Docetaxel Versus Doxorubicin in Patients With Metastatic Breast Cancer

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Purpose: **This phase III study compared docetaxel and doxorubicin in patients with metastatic breast cancer who had received previous alkylating agent–containing chemotherapy.**

Patients and Methods: **Patients were randomized to receive an intravenous infusion of docetaxel 100 mg/m^2 or doxorubicin 75 mg/m^2 every 3 weeks for a maximum of seven treatment cycles.**

Results: **A total of 326 patients were randomized, 165 to receive doxorubicin and 161 to receive docetaxel. Overall, docetaxel produced a significantly higher rate of objective response than did doxorubicin (47.8% *v* 33.3%; *P* = .008). Docetaxel was also significantly more active than doxorubicin in patients with negative prognostic factors, such as visceral metastases (objective response, 46% *v* 29%) and resistance to prior chemotherapy (47% *v* 25%). Median time to progression was longer in the docetaxel group (26 weeks *v* 21 weeks; difference not significant). Median overall survival was similar in the two groups (docetaxel, 15 months; doxorubicin, 14 months). There was one death due to infection in each group, and an additional four deaths due to cardiotoxicity in the doxorubicin group. Although neutropenia was similar in both groups, febrile neutropenia and severe infection occurred more frequently in the doxorubicin group. For severe nonhematologic toxicity, the incidences of cardiac toxicity, nausea, vomiting, and stomatitis were higher among patients receiving doxorubicin, whereas diarrhea, neuropathy, fluid retention, and skin and nail changes were higher among patients receiving docetaxel.**

Conclusion: **The observed differences in activity and toxicity profiles provide a basis for therapy choice and confirms the rationale for combination studies in early breast cancer.**

J Clin Oncol 17:2341-2354. © 1999 by American Society of Clinical Oncology.

DESPITE ADVANCES IN screening, locoregional treatment, and systemic adjuvant therapy for breast cancer, metastatic relapse is still common. The recent meta-analysis of adjuvant breast cancer trials indicated that after adjuvant polychemotherapy, 40% of patients had a recurrence, many of them, it can be assumed, with distant metastases.[1] For patients with advanced breast cancer whose tumors express the estrogen and/or progesterone receptor, endocrine therapy, as well as chemotherapy, can provide palliation, but for patients with receptor-negative cancers, those whose disease has become resistant to endocrine manipulations, and those in whom impending organ failure necessitates a rapid response, cytotoxic chemotherapy is generally the first treatment option to be considered.

Since its introduction in the early 1970s, doxorubicin has generally been considered to be the most active chemotherapeutic agent in the treatment of metastatic breast cancer. In particular, in patients with advanced breast cancer who have received previous alkylating agent chemotherapy, doxorubicin monotherapy has produced response rates of 25% to 33% at doses ranging from 60 to 75 mg/m^2, with median times to progression between 2.7 and 4.5 months.[2-7] Monotherapy with epirubicin or mitoxantrone[4,7-10] has not improved further the results obtained with doxorubicin as a single agent in this patient population.

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Submitted August 24, 1998; accepted March 30, 1999.

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0732-183X/99/1708-2341

Despite doxorubicin being considered standard treatment for advanced breast cancer, it is associated with a number of troublesome side effects that limit its use in the palliative setting; these include prominent myelotoxicity, nausea, vomiting, mucositis, and cumulative dose-dependent and generally irreversible cardiotoxicity.[11-15] The risk of developing congestive heart failure (CHF) increases from 7% at a total doxorubicin dose of 550 mg/m^2 to 15% at 600 mg/m^2 and 30% at 700 mg/m^2 [15]; however, CHF has also been reported at doses as low as 40 mg/m^2.[14] CHF typically becomes apparent 4 to 18 weeks after the last anthracycline dose, but it may occur during treatment or years later.[15]

The results of phase II clinical trials have shown that docetaxel (Taxotere; Rhône-Poulenc Rorer, Collegeville, PA; 100 mg/m^2/1-hour infusion) is a highly active agent for the treatment of patients with advanced breast cancer, including those with visceral involvement, liver involvement, and resistance to previous chemotherapy. Phase II studies in prospectively defined patient populations with and without previous anthracycline therapy yielded response rates of 43% and 61% and median times to progression of 4 and 5 months, in the respective patient populations.[16-18]

Docetaxel is associated with a cumulative toxicity, namely fluid retention. Docetaxel-related fluid retention is predictable (median dose to onset between 400 and 500 mg/m^2 in all phase II studies using corticosteroid premedication), reversible (median time to resolution between 16 and 20 weeks), and has not been lethal, with severe symptoms in only 5% to 6% of patients.[17-19]

To clarify the above observations, a phase III study comparing docetaxel with doxorubicin was performed to evaluate the benefit and risks of these two agents in the treatment of patients with advanced breast cancer who had received previous alkylating agent chemotherapy.

PATIENTS AND METHODS

Patient Population

Women with histologically or cytologically confirmed metastatic breast cancer who met the following eligibility criteria were included in the study: 18 to 75 years of age, measurable or nonmeasurable-but-assessable (evaluable) disease, performance status of at least 60 (Karnofsky index), and a life expectancy of at least 12 weeks. All patients had to have received previous alkylating agent chemotherapy (eg, cyclophosphamide, methotrexate, and fluorouracil [CMF], or its variants) either in the adjuvant setting or for advanced disease. Patients were classified as resistant or nonresistant to previous alkylating agent chemotherapy, as follows: resistant, relapse during or within 12 months of adjuvant therapy or progression during or within 30 days of last cycle of chemotherapy for advanced disease, regardless of response; nonresistant, relapse more than 12 months after adjuvant therapy or progression more than 1 month after last cycle of chemotherapy. Specific criteria for exclusion were as follows: more than one line of chemotherapy for advanced or metastatic disease; previous treatment with anthracyclines, anthracenes, or taxoids; no alkylating agent in last chemotherapeutic regimen; history or presence of brain or leptomeningeal metastases; previous or concurrent malignancies, with the exception of adequately treated in situ carcinoma of the uterine cervix and cured nonmelanoma skin cancer; inadequately assessable disease, defined as patients with only osteoblastic skeletal lesions, a single osteolytic lesion, lymphedema, pulmonary lymphangitic metastases, pleural effusion, and/or ascites as the only manifestation of disease; and symptomatic peripheral neuropathy of grade 2 or more according to National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Patients were also excluded if they had an absolute neutrophil count of less than 2×10^9/L, a platelet count below 100×10^9/L, a total bilirubin level above the upper normal limit (UNL); AST or ALT level more than three times the UNL and alkaline phosphatase level more than six times the UNL; AST or ALT more than 1.5 times the UNL and alkaline phosphatase level more than 2.5 times the UNL; serum creatinine level more than 1.5 times the UNL; a resting left ventricular ejection fraction (LVEF) of less than 50% (or below the lower normal limit of the institution) as measured by echocardiography or radionuclide angiocardiography. Concomitant bisphosphonate treatment was not allowed unless it had been initiated more than 3 months before the start of the study.

Patients were recruited from 41 centers worldwide. Ethics committee approval and informed patient consent were obtained before the start of the trial. Study investigators other than those listed as authors are shown in the Appendix.

Study Design

This was a randomized, multicenter, nonblinded, prospective, phase III study. The randomization was centralized and stratified for treatment arm by institution. There was no stratification for any prognostic factor. Patients were assigned randomly to receive an intravenous infusion of docetaxel 100 mg/m^2 for 1 hour every 3 weeks or doxorubicin 75 mg/m^2 for 15 to 20 minutes every 3 weeks. Premedication for hypersensitivity reactions and fluid retention was specified for patients in the docetaxel group only and consisted of oral dexamethasone 8 mg, given 13 hours, 7 hours, and 1 hour before docetaxel infusion and for a further 4 days at a dose of 8 mg twice daily, starting immediately after docetaxel infusion. Antiemetic premedication was given according to each center's normal practice. Prophylactic administration of granulocyte-colony stimulating factor (G-CSF) was not allowed in either treatment group.

The highest feasible dose of doxorubicin, without G-CSF support, was chosen to provide a reliable test of the single-agent activity of docetaxel. A maximum of seven treatment cycles was set for both groups because of the unacceptable incidence of CHF associated with a cumulative doxorubicin dose of more than 550 mg/m^2.[14] Fewer cycles were given if progression or unacceptable toxicity occurred. If a patient failed to respond to the assigned treatment, further treatment was at the discretion of the investigator. A decrease in LVEF of 10% (absolute units) in association with a decline below 50% (Schwartz criteria)[20] was specified as the criterion for treatment discontinuation based on LVEF assessments. Patients withdrawn from the study before progression could not receive other antitumor therapy until progression was documented, unless considered necessary by the investigator. Patients were observed for 1 month after their last study treatment infusion to document any late adverse events, with a follow-up visit every 3 months until death, to document time to progression (TTP) and survival.

Dose reductions were planned for severe hematologic and nonhematologic toxicities other than alopecia and anemia, graded according to NCI-CTC. A maximum of two dose reductions were allowed per patient, ie, from 100 to 75 mg/m^2 and from 75 to 55 mg/m^2 for docetaxel and from 75 to 60 mg/m^2 and from 60 to 45 mg/m^2 for doxorubicin.

Assessments

A complete tumor assessment, consisting of chest radiography and/or chest computed tomography scan, bone scintigraphy, bone radiography (if bone scintigraphy was positive), abdominal computed tomography or ultrasonography, and physical examination, was performed in the 3 weeks before the first infusion of study medication. Bone scintigraphy could be performed 4 weeks before the first infusion of study medication. All measurable and evaluable lesions were to be assessed at the end of cycles 2, 4, and 7 or at discontinuation of study treatment, and then at least every 3 months until progression in the follow-up period.

Response was classified according to World Health Organization criteria.[21] Complete response (no detectable tumor, including bone) and partial response ($\geq$ 50% reduction) had to be confirmed by a second evaluation more than 28 days later. Patients with no progression at least 6 weeks after the start of therapy were considered to have stabilization of disease. Patients with disease progression ($\geq$ 25% increase in size of any lesion or a new lesion) before or at the end of the second treatment cycle were considered to have early progression and were classified as having progressive disease for response to treatment. All patients with a radiographic record of tumor assessments were reviewed by an independent panel of two radiologists and an oncologist (the results of this review are reported).

Weekly blood counts were performed. Febrile neutropenia was defined as fever (38°C or more) with grade 4 neutropenia requiring intravenous antibiotics and/or hospitalization, without documented infection.

An initial assessment of LVEF was made during the 2 weeks before study entry, using a multiple gated angioscintigraphy (MUGA) scan or echocardiography; LVEF was re-assessed after a 400-mg/m^2 cumulative dose in the doxorubicin group, and when the patient stopped study treatment for any reason in either treatment group, using the same method as at baseline. No cumulative dose-specific evaluation was planned for the docetaxel arm because of the absence of cardiac toxicity in all previous reports. Fluid retention was monitored at each cycle and during follow-up until resolution. Severity of fluid retention was defined according to the following scale: mild, asymptomatic edema or effusion; moderate, edema that was pronounced or caused moderate functional impairment, or effusion that was symptomatic and possibly required drainage; and severe, edema that caused significant impairment or effusion causing dyspnea that required urgent drainage.

Quality of life (QOL) was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–C30, a 30-item core questionnaire,[22,23] which was completed by patients in the 3 days before their first infusion, before they received each cycle of study treatment, and at each visit during follow-up, up to and including the occurrence of first progression. The change in Karnofsky performance status (KPS) was used to assess patient condition from the physician's point of view.

Statistical Methodology and Analysis

The initial sample size of 156 patients per treatment group was selected to detect a 50% increase in median TTP with a 5% two-sided type I error and a 90% power. Accrual was expected to take 15 months. The sample size took into account the possibility that 10% of patients would not be assessable.

The intention-to-treat (ITT) population was defined as all randomized patients. The eligible and assessable population consisted of all patients who did not have a major deviation from the eligibility criteria, did not have an on-study deviation, received at least two cycles of treatment, and had at least one complete tumor assessment after the baseline evaluation. Analyses of response rate and TTP were performed on both the ITT population and on the eligible and assessable patient population. Analyses of survival and time to treatment failure (TTF) were performed on the ITT population only. Safety analyses were performed on all treated patients.

Response rate was defined as the percentage of patients in each treatment group who achieved a complete or partial response. TTP was calculated from the date of randomization until progression or death. Patients who received any further antitumor treatment before disease progression were censored at the date of the last tumor assessment before the start date of the new antitumor treatment. TTF was calculated from the date of randomization to the date of progression, death for any reason, withdrawal due to an adverse event, patient refusal, or further anticancer therapy before documentation of progression, whichever occurred first. Survival was calculated from the date of randomization to the date of death for any reason.

Categorical data, such as response rate and adverse events, were compared using the χ^2 test. Confidence intervals for response rates were computed using the exact method. Time-to-event parameters were analyzed using the Kaplan-Meier method. Efficacy parameters, such as TTP, TTF, and survival, were compared using the log-rank test and the Wilcoxon test. Multivariate analyses were performed on TTP, TTF, and survival using a Cox proportional hazards model and on response rate using a logistic regression model, to analyze the treatment effect when adjusting for prospectively chosen covariates (line of previous chemotherapy for advanced disease [none, one]; resistance to previous alkylating agents [not resistant, resistant]; age [$\leq$ 49 years, $\geq$ 50 years]; KPS [100%, 90% to 80%, $\leq$ 70%]; time from first diagnosis to randomization [$\leq$ 12 months, $>$ 12 months]; time from last chemotherapy to randomization [$\leq$ 3, 3 to 12, $>$ 12 months]; visceral, liver, or bone involvement [no, yes]; number of organs involved [1, 2, $\geq$ 3]; intention of previous hormonal therapy [none, adjuvant, advanced $\pm$ adjuvant]; number of lines of hormonal therapy for advanced disease [none, 1, $\geq$ 2]; previous chemotherapy received as adjuvant [no, yes]; setting(s) in which previous chemotherapy was received [adjuvant, advanced, adjuvant + advanced]; and baseline QOL score [continuous variable]) or for the most significant covariates using the Collett selection strategy.[24]

Safety analyses were performed on all treated patients. For hematologic and biochemical changes, drug safety was analyzed directly from reported laboratory parameters. Analysis of hematologic parameters was performed for treated patients who had at least one blood count assessed between the 2nd and 19th days of any cycle. Clinical signs and symptoms experienced on treatment were graded according to NCI-CTC or as mild, moderate, or severe (Coding Symbols for Thesaurus of Adverse Reaction Terms [COSTART] classification) if NCI-CTC were not appropriate.

Two types of analysis were performed on LVEF: relative decrease in LVEF from baseline according to the NCI-CTC, and absolute decrease in LVEF from baseline according to the Schwartz criteria, that is, a decrease in LVEF of at least 10 absolute percentage points and below the lower normal limit.

All ITT patients who had an assessable baseline questionnaire and at least one further measurable assessment on-study were considered assessable for QOL. The primary QOL variable was the global health score, and the principal secondary variable was the physical functioning score; the other 13 dimensions in the questionnaire were also analyzed. The Wilcoxon rank sum test was used to compare differences in the change from baseline to the average of the postbaseline measures between the two treatment groups. Median times to worsening of KPS by 20 points were analyzed by the Kaplan-Meier method.

In addition to the above analyses, which were proposed before initiation of the study, a sensitivity analysis was performed to examine the impact of missing data on the results. All QOL assessments within 6 months of randomization were included in the following analyses. Three methods were considered for the two major QOL measures: global QOL and physical functioning. All methods used a mixed effect model, which accommodated the mistimed QOL assessments. The first method assumes the data are missing at random.[25] Additional sensitivity analyses were performed using two different models assuming that the censoring was not random. The first of these methods is an example of a selection model.[26] The concept underlying this model is that patients whose QOL declines more rapidly are more likely to be censored earlier, either because of disease progression or death. The second method is an example of a pattern mixture model.[27] This model was estimated using the same mixed effects model within strata defined by a propensity score for dropout. Treatment group, prior chemotherapy, visceral involvement at baseline, performance status, and age predicted dropout before completion of seven cycles.

All analyses were performed using the SAS software package (SAS Institute, Cary, NC). All P values were two-sided. Differences at $P \leq .05$ were considered statistically significant.

RESULTS

Patients

Of the 326 patients randomized to receive study medication (docetaxel, n = 161; doxorubicin, n = 165), 159 patients in the docetaxel group and 163 patients in the doxorubicin group actually received treatment. The two patients in each group who did not receive study medication were included in the efficacy analyses, including the survival analysis.

The first patient was randomized on July 4, 1994, and the last on January 24, 1997. This report is based on data from all 326 randomized patients with follow-up until September 15, 1997. The median follow-up was 23 months, as determined by the reverse-survival Kaplan-Meier method.

In the docetaxel arm, four patients were considered ineligible: one patient had received two prior regimens of CMF for advanced disease, one patient had thrombocytopenia at baseline, one patient had a concomitant treatment with bisphosphonates started just before the study, and one patient had one lytic bone lesion as the only manifestation of disease. In the doxorubicin arm, six patients were considered ineligible: one patient had received two prior regimens for advanced disease, one patient had thrombocytopenia at baseline, one patient started treatment with bisphosphonates just before the study, one patient retrospectively had metastases from melanoma, one patient had only nonassessable lesions, and one patient did not receive an alkylating agent–containing regimen as the last chemotherapy.

There were no statistically significant differences in the pretreatment characteristics of the patients randomized to each group (Table 1). All patients had metastatic disease, and the most important negative prognostic factors (age < 50 years, visceral and liver involvement, involvement of three or more organs, previous adjuvant chemotherapy, and resistance to previous chemotherapy) were well represented and equal in the two groups. There was a slight imbalance in the proportions of patients with bone metastases (docetaxel, 55%; doxorubicin, 63%; $P = .12$). Slightly more patients in the docetaxel group had received previous chemotherapy in

Table 1. Baseline Characteristics of Randomized Patients

	Docetaxel (n = 161)		Doxorubicin (n = 165)	
	No.	%	No.	%
Age, years				
< 35	4	2	5	3
35-49	60	37	59	36
50-65	76	47	80	48
> 65	21	13	21	13
Age, years				
Median	52.0		52.0	
Range	32-74		25-74	
KPS				
Median	90		90	
Range	60-100		60-100	
No. of organs involved				
1	35	22	32	19
2	55	34	62	38
≥ 3	71	44	71	43
Sites of metastases				
Only soft tissue	14	9	20	12
Bone	89	55	104	63
Viscera	121	75	126	76
Liver	70	43	66	40
At least one measurable lesion	129	80	129	78
Intention of previous chemotherapy				
Adjuvant only	82	51	70	42
Relapse within 12 months	27	17	27	16
Relapse after 12 months	55	34	43	26
Advanced only	70	43	80	49
Adjuvant + advanced	9	6	15	9
Response to previous chemotherapy				
Resistant*	76	47	85	52
Not resistant†	85	53	80	48
Intention of previous hormonal therapy				
Adjuvant only	40	25	30	19
Advanced only	53	33	52	32
Adjuvant + advanced	20	12	33	20
Time from first diagnosis to first relapse, months				
Median	27		26	
Range	1-218		0-394	

*Relapse during adjuvant therapy, progression as best response, relapse within 12 months of end of adjuvant therapy, or progression during therapy after complete response, partial response, or no change.

†Relapse more than 12 months after adjuvant therapy or progression more than 1 month after complete response, partial response, or no change.

the adjuvant setting only; consequently, more patients in the doxorubicin group had received previous chemotherapy for advanced disease only, but the difference was not statistically significant ($P = .12$). As described in Statistical Methodology and Analysis, all prognostic factors were included in the multivariate analysis.

Exposure to Study Medication

The median number of treatment cycles administered was higher in the docetaxel group than in the doxorubicin group (seven cycles [range, one to 11] *v* six cycles [range, one to seven], respectively). The range of cycles exceeded seven in the docetaxel group because there were eight patients for whom the investigator considered continuation of treatment to be in their best interest. The median relative dose-intensity was 0.97 (range, 0.05 to 1.07) for docetaxel and 0.95 (range, 0.49 to 1.05) for doxorubicin.

Overall, 130 patients completed the maximum number of treatment cycles in accordance with the protocol, 74 in the docetaxel group and 56 in the doxorubicin group (46% *v* 34%, respectively; $P = .027$). Reasons for early discontinuation were as follows: disease progression (docetaxel, 30%; doxorubicin, 36%); adverse events (docetaxel, 12%; doxorubicin, 16%); withdrawal of consent (docetaxel, 3%; doxorubicin, 7%); death (docetaxel, 3%; doxorubicin, 2%); protocol violation (docetaxel, 1%; doxorubicin, 1%); and other (docetaxel, 5%; doxorubicin, 4%). Some patients in each group were still responding or had stable disease at the end of the seven treatment cycles planned in the protocol (doxorubicin, 45 patients [27%]; docetaxel, 58 patients, [36%]).

The adverse events that resulted most frequently in discontinuation in the doxorubicin group were cardiac toxicity (15 patients; 9%) and hematologic toxicity (six patients; 4%). In the docetaxel group, the most frequent were neurologic toxicity (five patients; 3%), allergy (three patients; 2%), and peripheral edema (three patients; 2%). Of the 15 patients who discontinued doxorubicin treatment because of cardiac toxicity, three withdrew because of clinical CHF; the other 12 patients had a decrease in LVEF according to the Schwartz criteria. Two of these patients developed clinical CHF during follow-up. Another patient who developed clinical CHF during follow-up did not discontinue because of cardiac toxicity. Patients who experienced a decrease in LVEF meeting the Schwartz criteria but did not discontinue because of cardiac toxicity, had the decrease assessed at treatment completion or discontinuation for a reason other than cardiac toxicity.

Fewer treatment cycles were delayed by at least 3 days in the docetaxel group than in the doxorubicin group (7% *v* 15%, respectively). In addition, fewer treatment cycles were delayed because of treatment-related adverse events in the docetaxel group (21 cycles, 2%, *v* 89 cycles, 11%, respectively). Specifically, hematologic toxicity (mostly low neutrophil counts) was the reason for treatment delay in six patients (3.7%) and nine cycles (0.9%) in the docetaxel group and in 43 patients (26.3%) and 69 cycles (8.2%) in the doxorubicin group.

The study medication dose was reduced at least once in a similar number of treatment cycles in each group (docetaxel, 47 cycles, 5%; doxorubicin, 40 cycles, 5%). The main reason for dose reduction was hematologic toxicity (65% of dose-reduced cycles in the doxorubicin group and 45% of dose-reduced cycles in the docetaxel group).

Efficacy

The overall response rate (complete responses plus partial responses) was significantly higher with docetaxel than with doxorubicin for both randomized (47.8% *v* 33.3%, respectively; $P = .008$) and assessable patients (52.0% *v* 37.4%, respectively; $P = .012$; Table 2). The difference in the overall response rate between the two treatment arms was 14.5% (95% confidence interval [CI], 3.9% to 25.0%). The complete response rate was higher in the docetaxel group than in the doxorubicin group, and fewer patients in the docetaxel group had progressive disease without any response or stabilization. In the multivariate analysis, a significant treatment effect in favor of docetaxel was seen when adjusting for all covariates (odds ratio, 1.8; 95% CI, 1.1 to 2.9; $P = .024$) or for the most important ones using the Collett strategy (odds ratio, 1.7; 95% CI, 1.1 to 2.8; $P = .027$). The variables identified for inclusion in the Collett

Table 2. Response to Treatment

Efficacy Variable	Randomized Patients (%)		Assessable Patients (%)	
	Docetaxel (n = 161)	Doxorubicin (n = 165)	Docetaxel (n = 148)	Doxorubicin (n = 147)
Response to treatment				
Complete response	6.8	4.2	7.4	4.8
Overall response rate*	47.8	33.3	52.0	37.4
95% CI	40.1%-55.5%	26.1%-40.5%	44.0-60.1%	29.6%-45.2%
Progression	12.4	22.4	12.2	23.8
Not assessable	5.6	6.7	—	—

*Overall response rate includes complete responses plus partial responses ($P = .008$ for randomized patients, $P = .012$ for assessable patients).

analysis of response rate were time from last chemotherapy to randomization, baseline QOL score, intent of prior chemotherapy, bone involvement, and treatment arm. Docetaxel produced a higher response rate than doxorubicin in almost all subgroups analyzed, especially in patients with a poor prognosis because of liver involvement or resistance to previous alkylating agents (Fig 1). All patients had normal liver functions or mildly abnormal liver functions, as stated in the protocol entry criteria, thus representing docetaxel effectiveness in patients with liver metastases and relatively normal liver function.

Median TTP was longer in the docetaxel group than in the doxorubicin group for both randomized (26 weeks *v* 21 weeks, respectively; Fig 2) and assessable patients (27 weeks *v* 23 weeks, respectively), although the difference between treatment groups did not reach statistical significance according to either the log-rank or Wilcoxon test. In the multivariate analysis, no significant difference was found in TTP between the two groups when adjusting for all covariates or for the most important ones (risk ratio, 1.0; 95% CI, 0.8 to 1.3). As noted above, eight patients in the docetaxel group received more than seven cycles. An additional analysis of TTP, censoring these patients at cycle 7, produced the same results.

Median TTF was longer in the docetaxel group (22 weeks) than in the doxorubicin group (18 weeks); the difference between groups was significant according to the Wilcoxon test ($P = .0137$) but not by the log-rank test (Fig 3). In the multivariate analysis, there was no significant difference between the two groups when adjusting for all covariates or for the most important ones (risk ratio, 1.1; 95% CI, 0.9 to 1.4).

The most important variables identified for the Collett analysis of TTP, TTF, and survival were performance status, baseline QOL score, time from last chemotherapy to randomization, and number of organs involved (number of organs involved was not selected for TTF).

The median overall survival of all randomized patients was similar in the two treatment groups (docetaxel, 15 months; doxorubicin, 14 months; Fig 4). In the multivariate analysis, no significant difference was found between the two groups when adjusting for all covariates or for the most important ones (risk ratio, 1.0; 95% CI, 0.8 to 1.3). No cross-over was planned, but 26% of patients in the doxorubicin group received taxoid-containing therapy, and 28% of patients in the docetaxel group received anthracycline-containing therapy as the first anticancer treatment after study treatment. No activity or safety data regarding the cross-over treatments were collected. The difference between treatment groups remained not significant when overall survival was adjusted for the cross-over treatment as a time-dependent covariate.

Safety

The incidence of toxic deaths was higher in the doxorubicin group (3%) than in the docetaxel group (1.2%). Five patients died in the doxorubicin group: one death occurred due to infection within 30 days of the last infusion; the

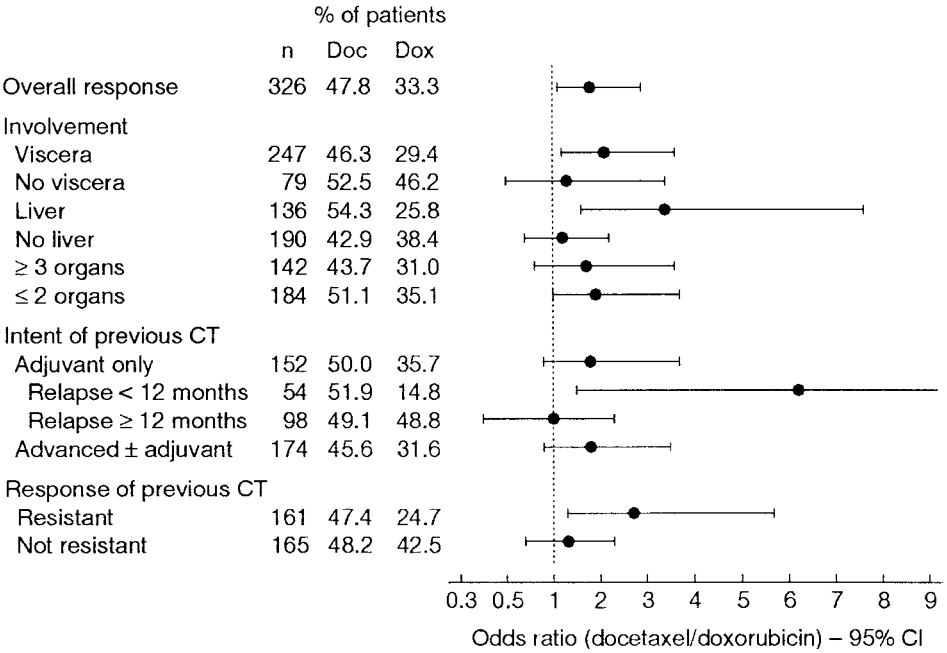

Fig 1. Odds ratio of response, docetaxel versus doxorubicin (Doc, docetaxel; Dox, doxorubicin; CT, chemotherapy).

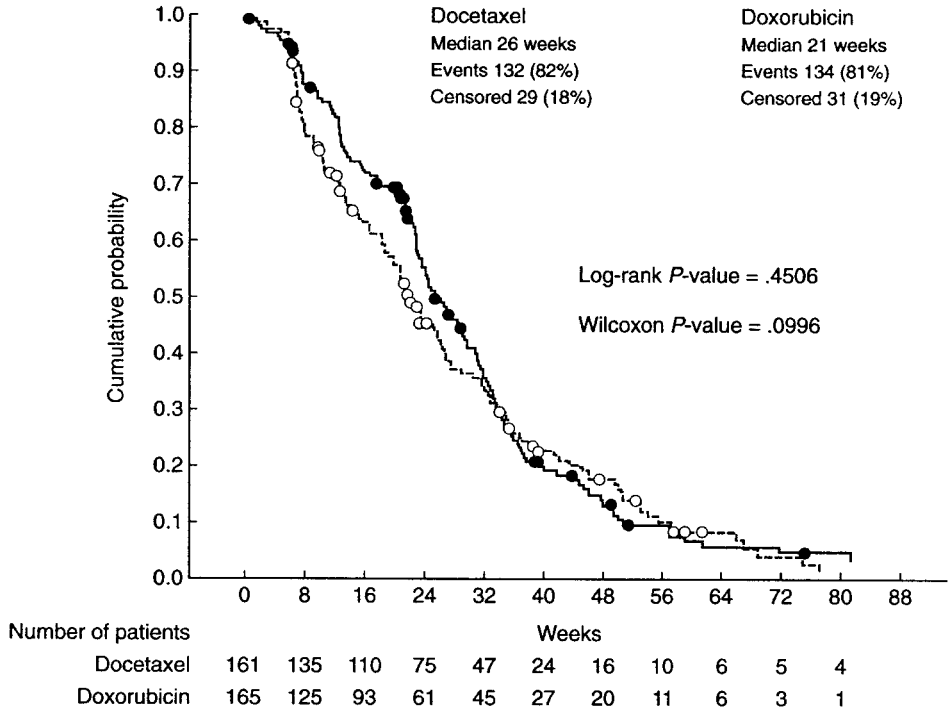

Fig 2. Kaplan-Meier estimate of the cumulative probability of remaining free from disease progression in each treatment group (ITT population) (docetaxel, n = 161, ●; doxorubicin, n = 165, ○).

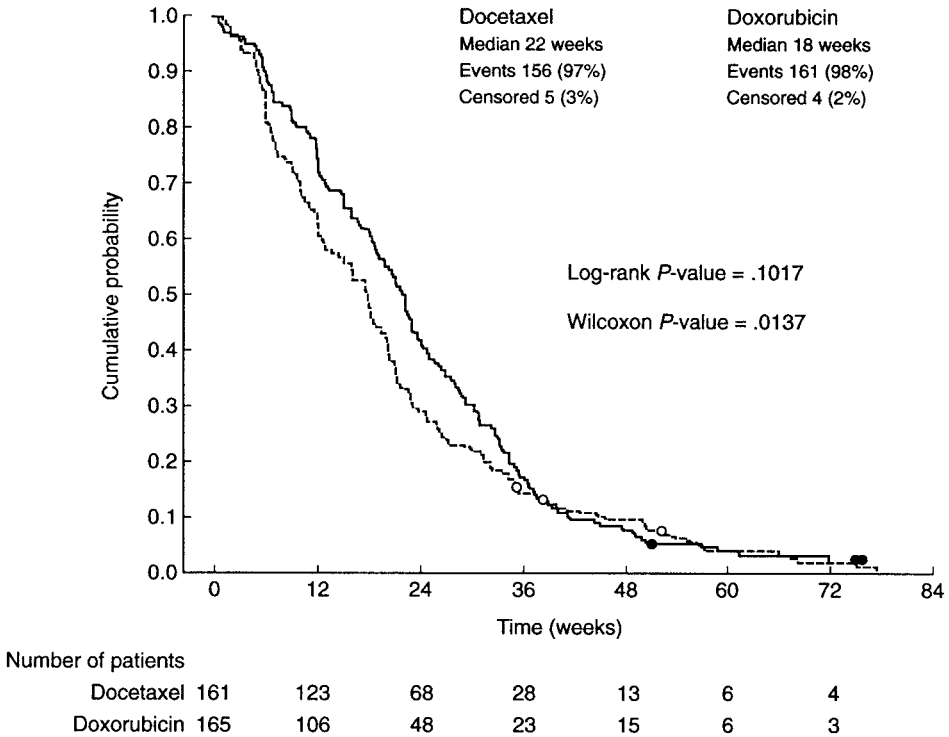

Fig 3. Kaplan-Meier estimate of the cumulative probability of remaining free from treatment failure in each treatment group (ITT population) (docetaxel, n = 161, ●; doxorubicin, n = 165, ○).

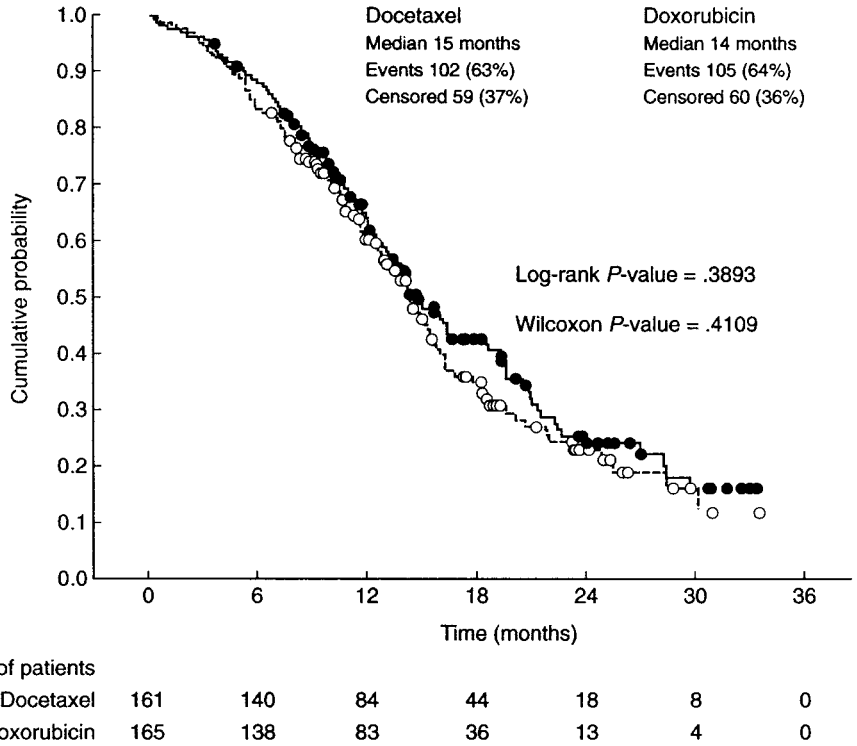

Fig 4. Kaplan-Meier estimate of the cumulative probability of survival in each treatment group (ITT population) (docetaxel, n = 161, ●; doxorubicin, n = 165, ○).

remaining four patients died due to doxorubicin-related cardiac toxicity more than 30 days after the last infusion (three patients developed CHF at cumulative doxorubicin doses of 387, 437, and 450 mg/m^2, and one patient with a history of hypertension and cardiomegaly on pretreatment chest x-ray developed tachycardia at the same time as disease progression [including pericarditis carcinomatosa] at a cumulative doxorubicin dose of 536 mg/m^2). In the docetaxel group, one patient died due to infection, and one died due to disease progression associated with liver failure in a patient whose liver enzyme levels rose above entry level eligibility in the week between randomization and first treatment and in whom the contribution of treatment to the onset of liver failure could not be ruled out.

Hematologic adverse events related to study medication are presented in Table 3. Grade 4 neutropenia was the most frequent hematologic toxicity and was similar in both groups; however, the incidence of severe neutropenic complications (febrile neutropenia and severe infection) was significantly higher in the doxorubicin group (doxorubicin, 16%; docetaxel, 8%; $P = .02$). The median time to neutropenic nadir was 7 days (range, 5 to 15 days) in the docetaxel group and 14 days (range, 7 to 19 days) in the doxorubicin group. The time taken to recover from neutropenic nadir to grade 0 or 1 neutropenia was 7 days in both treatment groups. However, the fact that the study design required only weekly blood counts limits this analysis. The incidence of grade 3 or 4 anemia was significantly higher in the doxorubicin group, as was the proportion of patients who required an RBC transfusion. Thrombocytopenia (overall and severe) was significantly more frequent in the doxorubicin group but did not induce significant clinical complications.

Nonhematologic adverse events related to study medication are presented in Table 4. Nausea, vomiting, and stomatitis occurred more frequently in the doxorubicin group, whereas diarrhea, skin toxicity, allergy, nail disorder, and neurotoxicity occurred more frequently in the docetaxel group. The incidences of asthenia and alopecia were similar in the two groups.

With regard to dose-cumulative toxicities (Table 5), fluid retention in the docetaxel group was counterbalanced by cardiac toxicity in the doxorubicin group. Six patients (3.7%) in the doxorubicin group developed CHF (three during treatment and three during follow-up; Table 6). All of these patients had received a cumulative doxorubicin dose below what is normally considered a safe dose ($<$ 460 mg/m^2), and only one patient had risk factors in her history (73 years of age and hypertension). Among the 86 patients being treated with docetaxel who were assessable for LVEF decrease, 57% were evaluated by MUGA scan, and among the 101 patients who were assessable in the doxorubicin treatment arm, 54% were evaluated by MUGA scan. The remainder of patients, on both arms, assessable for LVEF

Table 3. Hematologic Adverse Events

Adverse Event	Docetaxel		Doxorubicin	
	No. of Patients	%*	No. of Patients	%*
Neutropenia				
Overall	154	97.4	153	96.7
Grade 3	154	14.9	153	11.1
Grade 4	154	78.6	153	77.8
Febrile neutropenia†	159	5.7‡	163	12.3
Infection grade 3/4	159	2.5	163	4.3
Anemia				
Overall	158	88.6	161	93.2
Grade 3/4	158	4.4‡	161	16.1
RBC transfusion	159	6.9‡	163	20.9
Thrombocytopenia				
Overall	158	4.4‡	161	40.4
Grade 4	158	1.3‡	161	7.5

*Incidence of events possibly/probably related to study medication.

†Fever ≥ grade 2 and grade 4 neutropenia requiring hospitalization and/or intravenous antibiotics.

‡$P \leq .05$.

were assessed by echocardiography at all assessments. Of the 29 patients in the doxorubicin group who had a reduction in LVEF that met the Schwartz criteria, only 10 had received a cumulative doxorubicin dose of 460 mg/m^2 or more; 16 had no risk factors for CHF, five had a history of hypertension, four had an effusion (pericardial or pleural) related to disease, three had radiotherapy to the left breast, and one had mediastinum tumor involvement. Of note, 20 of the 29 patients were detected after seven cycles.

Of the seven patients in the docetaxel group who had a reduction in LVEF that met the Schwartz criteria, three had a concomitant medical condition that may have accounted for the decrease in LVEF (hypertension, radiotherapy of the left chest wall that may have encompassed the heart, and concomitant grade 4 pericardial effusion).

Table 4. Nonhematologic Adverse Events

Adverse Event	% of Patients†			
	Overall % of Patients*		% of Patients With Grade 3/4 or Severe Events	
	Docetaxel (n = 159)	Doxorubicin (n = 163)	Docetaxel (n = 159)	Doxorubicin (n = 163)
Acute				
Nausea	39.6†	79.1	3.1†	14.1
Vomiting	22.6†	58.3	3.1†	12.3
Stomatitis	49.7	58.3	5.0†	12.3
Diarrhea	50.3†	17.2	10.7†	1.2
Skin toxicity	37.7†	7.4	1.9	0.6
Allergy	17.6†	5.5	2.5	1.2
Chronic				
Alopecia	91.2	90.8	NA	NA
Asthenia	59.7	56.4	14.5	12.3
Nail disorder	44.0†	4.9	2.5	0
Neurosensory	42.8†	5.5	5.0	0
Neuromotor	18.2†	2.5	5.0	0

*Incidence of events possibly/probably related to study medication.

†$P \leq .05$.

Table 5. Cumulative Toxicities

	Docetaxel Patients (n = 159) (%)	Doxorubicin Patients (n = 163) (%)
Cardiac toxicity		
CHF	0	3.7
LVEF decrease (Schwartz)*	8.1	28.7
LVEF decrease > 20%*	8.1	31.7
LVEF decrease > 40%*	0	16.0
Discontinuation rate	0	9.2
Lethal	0	1.8
Fluid retention		
Overall	59.7	4.3
Severe	5.0	0
Discontinuation rate	1.9	0
Lethal	0	0
Median time to recovery, weeks	19	NA

Number of patients assessable for LVEF: docetaxel, n = 86; doxorubicin, n = 101.

In the docetaxel group, the median cumulative dose to onset of fluid retention was 478 mg/m^2 (range, 5^+ to 892^+ mg/m^2). Of the 95 patients who experienced fluid retention, 74.7% experienced edema only, 15.8% experienced edema and weight gain, and 6.3% experienced edema and pleural effusion, and the remaining patients comprised individual cases of all three symptoms, weight gain only, and edema and pericardial effusion.

QOL

Overall compliance (defined as the ratio between the number of patients assessable for QOL and the number of patients on treatment at each cycle) was high (> 80%) and similar in both groups for cycles 1 to 4, but it deteriorated in the doxorubicin group at cycle 5 (docetaxel, 86%; doxorubicin, 64%) and remained higher in the docetaxel group at cycle 6 (74% *v* 69%, respectively). The cumulative proportion of missing scores at each cycle (attrition rate) was

Table 6. Patients With CHF in the Doxorubicin Group

Patient No.	Days From Last Treatment to CHF Onset	Total Cycles Received	Cumulative Dose (mg/m^2)	Outcome	Baseline LVEF (%)	LVEF (%) at Onset of CHF
1	15	6	437	Death*	54	35†
2	52	7	449	Improved	76	Not done
3	98	5	387	Death*	53	23†
4	197	6	450	Death*	65	Not done
5	44	6	454	Ongoing	70	23
6	39	6	456	Improved	60	47†

*More than 30 days after last infusion.

†Confirmed with repeated-measure analysis.

higher in the doxorubicin group than in the docetaxel group (eg, 34% *v* 25% and 56% *v* 43% at cycles 4 and 6, respectively).

Mean decreases in global health and physical functioning scores from baseline were not significantly different in the two treatment groups (Fig 5). The median time to worsening of the KPS by 20 points was not reached in either treatment group, and changes from baseline per cycle were similar in the two treatment groups; most patients (approximately 80%) had a stable KPS.

As described in Statistical Methodology and Analysis, supplementary analyses were performed to examine the sensitivity of the results to different assumptions about the missing data, and specifically to consider the possibility of nonignorable (nonrandom) censoring in the QOL assessments. In comparisons of the two treatment groups, no statistically significant treatment effect was found in global QOL or physical functioning at 13, 19, or 26 weeks after randomization across any of the three methods considered (results not shown). The results of the three analytical models on global QOL score do not show statistical evidence in the data for nonrandom missingness, and the estimates were stable across all analyses. It should be emphasized, however, that the lack of statistical evidence in the available data does not rule out the possibility of nonrandom dropout throughout the study.

DISCUSSION

This is the first randomized trial in metastatic breast cancer in which a chemotherapeutic agent (docetaxel 100 mg/m^2/1-hour infusion) has produced a significantly higher response rate than doxorubicin given at its highest feasible dose (75 mg/m^2/short intravenous infusion) without growth factors.

The difference between docetaxel and doxorubicin was confirmed by the logistic regression model on response rate; the odds for response in a patient receiving docetaxel were 1.7 times higher than in a patient receiving doxorubicin (adjusting for most important prognostic factors). A higher probability of response may be of particular clinical impor-

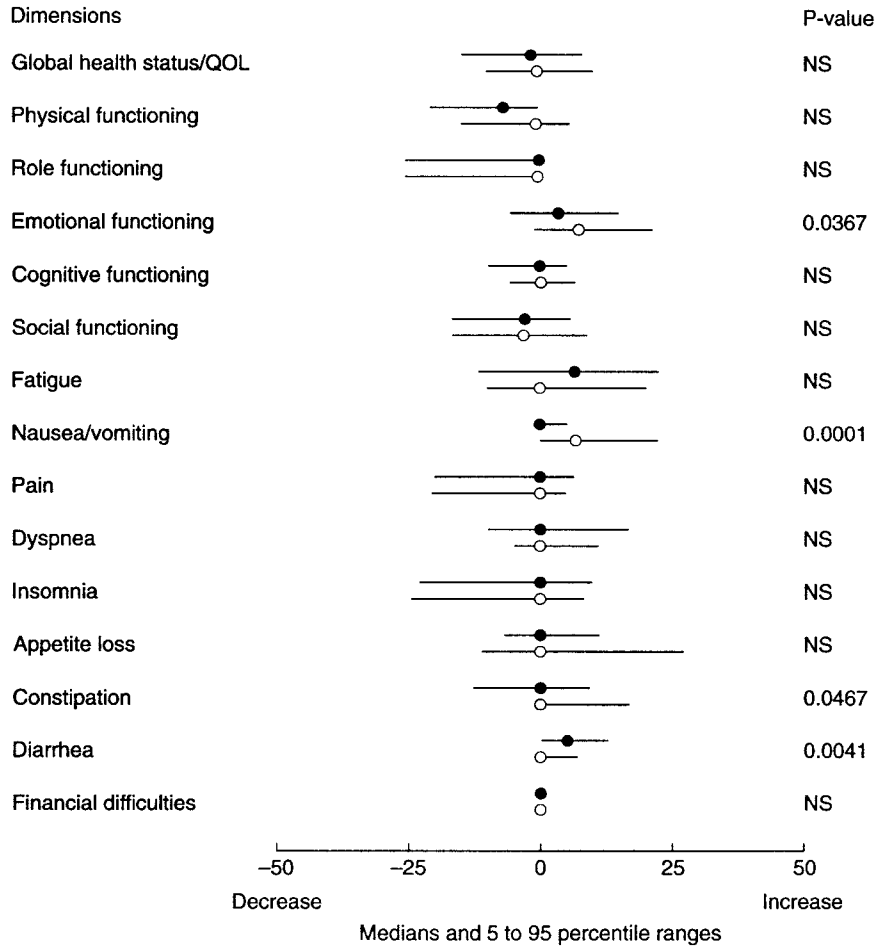

Fig 5. Medians of the mean changes in QOL scores from baseline (all assessable patients) (docetaxel, n = 142, ●; doxorubicin, n = 143, ○).

tance in patients with liver metastases (before significant liver impairment) or symptoms requiring urgent attention, such as dyspnea caused by lymphangitic carcinomatosis. In patients with rapidly deteriorating liver function tests, the values should be re-assessed on the day of treatment to confirm that these patients remain candidates for treatment. In addition, more patients in the doxorubicin group had progression of disease without any response or stabilization of disease.

While a statistically significant difference in response rate was shown, the study was powered to detect a difference of 50% in median TTP as the primary end point. A 25% difference in favor of docetaxel was shown, but this did not reach statistical significance as assessed by log-rank or Wilcoxon test. TTF was statistically significantly in favor of docetaxel by the Wilcoxon test (which gives more weight to the earlier events with larger patient numbers), but it was not significant as assessed by the log-rank test. Overall survival was not different between the two groups.

The results of our study confirm the activity of docetaxel 100 mg/m^2 reported in phase II studies. In five phase II studies with a total of 154 patients untreated for metastatic disease, docetaxel yielded a response rate of 61% (95% CI, 52% to 69%), with a median TTP of 4.9 months and a median survival time of 16.4 months. In addition, in four phase II studies involving a total of 134 patients resistant to anthracyclines, docetaxel produced a response rate of 43% (95% CI, 35% to 50%), with a median TTP of 4.3 months and a median survival time of 10.6 months (ITT analysis).[16]

This study has shown that docetaxel has a consistently high level of activity in patients with metastatic breast cancer, regardless of negative prognostic factors; this was not the case for doxorubicin. For example, docetaxel produced similar response rates in patients resistant and nonresistant to a prior CMF regimen (47% and 48%, respectively); doxorubicin, however, was less effective in resistant patients than in nonresistant patients (25% *v* 43%, respectively). This observation suggests that docetaxel does not have clinical cross-resistance to previous CMF regimen.

The median TTP was longer in the docetaxel group, although the difference was not statistically significant (according to both log-rank test and multivariate analysis). The shape of the curve (Fig 2) suggests that fewer patients receiving docetaxel are likely to experience progression in the first few treatment cycles, as compared with patients receiving doxorubicin. This is supported by the results of the Wilcoxon test, which were close to being significant, although in the context of multiple testing.

The term treatment failure encompasses discontinuation because of toxicity, in addition to disease progression (which is described more specifically by TTP), and may therefore provide a clinically important measurement of the time that the patient is receiving, and possibly benefiting from, treatment. In our study, the median TTF was longer in the docetaxel group than in the doxorubicin group; the difference was statistically significant according to the Wilcoxon test ($P = .0137$). The lower probability of failure in the first few months of docetaxel therapy may reflect some benefit over doxorubicin for the patient, but this was not seen in the QOL results of our study. Further QOL studies focusing on the moment when treatment failure occurs and the period immediately afterward may be able to quantitate just how meaningful this difference is to the patient.

The high rate of attrition limits interpretation of changes in QOL scores from baseline, and any conclusions are therefore drawn with caution. With these limitations, however, the evolution of QOL was not clinically significantly different in the two groups and was relatively stable for the entire duration of the two study treatments. In particular, it was notable that the longer length of exposure to study medication in the docetaxel group did not have a negative impact on QOL. To ensure that more meaningful data are obtained from future studies using QOL measurements, we suggest that particular attention is paid to compliance at the time of progression or early study discontinuation.

Our comparison of safety parameters favored docetaxel. First, there were more toxic deaths in the doxorubicin group than in the docetaxel group. In addition, doxorubicin-related cardiac toxicity was in some cases life-threatening, unpredictable, and irreversible: clinical CHF was observed in six doxorubicin patients at cumulative doses below 460 mg/m^2, which is commonly considered to be a safe cumulative dose.

Cardiac toxicity was also the most frequent reason for discontinuation of doxorubicin treatment. The dose-cumulative LVEF evaluation required for doxorubicin only may have introduced a bias in these results. However, for docetaxel patients, the low incidence of any LVEF decreases (assessed at end of treatment) and the absence of any CHF (assessed throughout the study) confirm that cardiac toxicity is not associated with docetaxel and cardiac monitoring is not required. In contrast, docetaxel-related fluid retention was less likely to lead to treatment discontinuation and did not cause any mortality.

As expected for the other nonhematologic toxicities, doxorubicin patients experienced nausea, vomiting, and stomatitis most frequently, whereas docetaxel patients experienced diarrhea, neurotoxicity, and skin and nail changes most frequently. The lack of overlap in the nonhematologic toxicities of docetaxel and doxorubicin suggests that these two agents may be combined. Safety differences should be taken into consideration when deciding on which drug is an appropriate option for use as monotherapy.

Although the incidence of grade 4 neutropenia is similarly high with both drugs, docetaxel induces fewer neutropenic complications (febrile neutropenia and severe infections). This observation may be explained by the higher level of stomatitis (overall and severe) in the doxorubicin group and by the different neutropenic profiles as indicated by the median number of days to nadir and the number of cycles requiring treatment delay for hematologic reasons.

While the results of this study reflect a well-designed trial based on data available at that time, there are two areas where current clinical practice may not be reflected. The first relates to the safety profile of docetaxel reported in our study, which is for patients who had received a 5-day regimen of corticosteroid premedication; a 3-day regimen is now known to be equally effective and improves the overall safety profile of docetaxel, particularly with regard to mucositis, diarrhea, and infection.[19] The second area of difference relates to the seven-cycle limit, which was necessary because of the cumulative toxicity of doxorubicin and was imposed in both treatment groups to provide a balanced study. In the docetaxel group, over 50 patients were still responding when treatment was stopped in accordance with the protocol. Continuation of treatment with docetaxel is an option because of the low rate of discontinuation due to fluid retention associated with cumulative dose. Further studies are needed to determine whether additional cycles are beneficial and produce improvements in TTP and survival times. Duration of therapy may be an important variable not considered in this study; indeed, it has been found to have an effect in other studies with various chemotherapy regimens.[28-30]

There is no published controlled randomized trial comparing 60 and 75 mg/m^2 of doxorubicin in metastatic breast cancer. There is a small phase II comparison by Carmo-Pereira et al[31] in which they report a significant difference in response rates and survival when comparing 35 mg/m^2/3 weeks (16 cycles) with 70 mg/m^2/3 weeks (eight cycles). The 75-mg/m^2 dose of doxorubicin was chosen because on the basis of previous reports, it seemed to have a neutropenia level similar to that of docetaxel at 100 mg/m^2; neutropenia is considered by some to be a surrogate for activity. Doxorubicin 75 mg/m^2 is the highest feasible dose without growth factors. The results of our study show a similar incidence and severity of neutropenia for both treatment arms, confirming this to be a comparison of equineutropenic doses.

Studies comparing nonanthracycline, single-agent chemotherapy with doxorubicin monotherapy are rare. To our knowledge, there is only one published large phase III trial comparing doxorubicin with a nonanthracycline agent in a patient population similar to ours.[7] Doxorubicin 75 mg/m^2/3 weeks was compared with mitoxantrone 14 mg/m^2/3 weeks in advanced breast cancer patients who had received a previous alkylating agent–containing regimen. The overall response rate was 29% in the doxorubicin group and 21% in the mitoxantrone group, and the median TTP was 16 weeks in the doxorubicin group and 11 weeks in the mitoxantrone group. The response rate and median TTP produced by docetaxel in our study compare favorably with these results.

The taxoid paclitaxel has also been compared with doxorubicin in two recently reported, large-scale phase III randomized studies.[32,33] The first study was conducted by the EORTC and compared paclitaxel 200 mg/m^2/3-hour infusion with doxorubicin 75 mg/m^2.[32] Of the 331 patients recruited, 68% were chemotherapy-naive and the remaining 32% had received alkylating agent chemotherapy with adjuvant intent. In our study, the patient population was more heavily pretreated (all patients had received alkylating agent chemotherapy with adjuvant intent or for advanced disease, or both). In the EORTC study, doxorubicin produced a significantly higher response rate (41% *v* 25%; $P = .003$) and longer median progression-free survival time (7.5 months *v* 4.2 months; $P < .001$) than paclitaxel. Median survival duration also favored doxorubicin (18 months *v* 15 months); the difference in survival was not significantly different ($P = .20$).

The second study was a three-arm North American trial in which doxorubicin 60 mg/m^2 was compared with paclitaxel 175 mg/m^2/24-hour infusion as well with the combination of doxorubicin 50 mg/m^2 plus paclitaxel 150 mg/m^2/24-hour infusion with G-CSF, in patients with advanced breast cancer.[33] Of 739 patients randomized, 69% were chemotherapy-naive and 31% had received chemotherapy with adjuvant intent. Although the patients were less heavily pretreated than in our study and a lower doxorubicin dose was used, the response rate for paclitaxel in the assessable population achieved only parity with that for doxorubicin (34% *v* 36%, respectively).

A number of features confound any comparison of these studies with ours, and no conclusions can be drawn from this type of indirect comparison; the studies are reviewed merely as a background perspective to our finding that docetaxel produces a significantly higher response rate than doxorubicin. In this regard, the results of an ongoing direct comparison of paclitaxel with docetaxel are awaited.

In conclusion, docetaxel given at its highest feasible dose without G-CSF is at least as appropriate as doxorubicin given at its highest feasible dose without G-CSF for patients with metastatic breast cancer. Studies evaluating docetaxel in the classic combination approach with doxorubicin or in a sequential schedule are clearly warranted. The rapid development of docetaxel for patients with early breast cancer should be a clinical research priority.

APPENDIX
Other Study Participants

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