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Improved Outcomes From Adding Sequential Paclitaxel but Not From Escalating Doxorubicin Dose in an Adjuvant Chemotherapy Regimen for Patients With Node-Positive Primary Breast Cancer

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Purpose: **This study was designed to determine whether increasing the dose of doxorubicin in or adding paclitaxel to a standard adjuvant chemotherapy regimen for breast cancer patients would prolong time to recurrence and survival.**

Patients and Methods: **After surgical treatment, 3,121 women with operable breast cancer and involved lymph nodes were randomly assigned to receive a combination of cyclophosphamide (C), 600 mg/m², with one of three doses of doxorubicin (A), 60, 75, or 90 mg/m², for four cycles followed by either no further therapy or four cycles of paclitaxel at 175 mg/m². Tamoxifen was given to 94% of patients with hormone receptor–positive tumors.**

Results: **There was no evidence of a doxorubicin dose effect. At 5 years, disease-free survival was 69%, 66%, and 67% for patients randomly assigned to 60, 75, and 90 mg/m², respectively. The hazard reductions from adding paclitaxel to CA were 17% for recurrence (adjusted Wald χ^2 *P* = .0023; unadjusted Wilcoxon *P* = .0011) and 18% for death (adjusted *P* = .0064; unadjusted *P* = .0098). At 5 years, the disease-free survival (± SE) was 65% (± 1) and 70% (± 1), and overall survival was 77% (± 1) and 80% (± 1) after CA alone or CA plus paclitaxel, respectively. The effects of adding paclitaxel were not significantly different in subsets defined by the protocol, but in an unplanned subset analysis, the hazard ratio of CA plus paclitaxel versus CA alone was 0.72 (95% confidence interval, 0.59 to 0.86) for those with estrogen receptor–negative tumors and only 0.91 (95% confidence interval, 0.78 to 1.07) for patients with estrogen receptor–positive tumors, almost all of whom received adjuvant tamoxifen. The additional toxicity from adding four cycles of paclitaxel was generally modest.**

Conclusion: **The addition of four cycles of paclitaxel after the completion of a standard course of CA improves the disease-free and overall survival of patients with early breast cancer.**

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ADJUVANT SYSTEMIC therapy with the drug combination cyclophosphamide, methotrexate, and fluorouracil (CMF) reduces the annual odds of recurrence and death of patients with early breast cancer (± SD) by 24% (± 3%) and 14% (± 4%), respectively.[1] An overview of trials in which an anthracycline, either doxorubicin or epirubicin, was added to cyclophosphamide (with or without a vinca alkaloid, methotrexate, or fluorouracil) demonstrated that the anthracycline regimens resulted in a reduction in annual odds (± SD) of 12% (± 4%) and 11% (± 5%) in recurrence or death, respectively, compared with CMF.[1] One of the earliest and largest of these studies compared 3 months (four cycles) of cyclophosphamide plus doxorubicin (CA) with 6 months of CMF and failed to show any significant differences in outcome.[2] Because the CA regimen used a shorter duration of therapy and was thus perceived as being less toxic, four cycles of CA became one of the most commonly used adjuvant therapy regimens in the United States before the overview that demonstrated the superiority of anthracycline regimens was performed.

The trial reported here was designed to see whether the benefits from four cycles of CA could be increased either by doxorubicin dose escalation or by adding paclitaxel, a drug known to be non–cross-resistant with anthracyclines.[3-6] Decreasing the doses of doxorubicin, cyclophosphamide, and fluorouracil below standard levels has been shown to compromise the benefits from adjuvant chemotherapy,[7,8] but two studies evaluating cyclophosphamide dose escalation above standard levels have failed to demonstrate additional benefit.[9,10] Neither doxorubicin dose escalation nor the use of a taxane has previously been evaluated in the adjuvant setting. To evaluate both questions in one trial, we used a 3 × 2 factorial design.[11] Three

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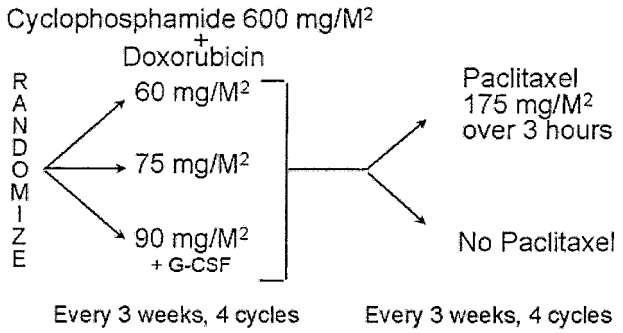

Fig 1. Protocol schema; 3 × 2 factorial design. After completion of chemotherapy, radiation therapy was administered if patient was treated with lumpectomy or at discretion of physician if patient was treated with masectomy, and tamoxifen 20 mg/d was administered for 5 years if the tumor was receptor positive.

doxorubicin doses were used to allow for estimating the slope of the dose-response curve and to identify any dose that might skew an estimate of dose effect because it is on a threshold or at a plateau of the dose-response curve. After completion of four cycles of CA, patients were randomly assigned to receive either no further treatment or four cycles of paclitaxel at 3-week intervals.

PATIENTS AND METHODS

This was an Intergroup trial (INT 0148) conducted at 516 sites and coordinated by the Cancer and Leukemia Group B (CALGB 9344). Other participants were the Eastern Cooperative Oncology Group, the Southwest Oncology Group, and the North Central Cancer Treatment Group.

Eligible patients had operable breast cancer with clear surgical margins and metastases to axillary nodes. Initial surgical treatment was either mastectomy or lumpectomy with axillary lymph node sampling. Radiotherapy to the breast was required for all patients treated with less than a mastectomy and was begun after all chemotherapy had been administered. The study had to be approved by the institutional review board at each institution enrolling patients, and all patients were required to provide written informed consent before being registered on the study.

Systemic therapy was to have begun within 84 days of the patient's last surgery. All patients received 600 mg/m^2 of cyclophosphamide intravenously on day 1 and were randomly assigned to one of three doxorubicin doses given on day 1 (60 mg/m^2) or days 1 and 2 (75 and 90 mg/m^2; Fig 1). Filgrastim (granulocyte colony-stimulating factor [G-CSF]), 5 μg/kg/d, and ciprofloxacin, 750 mg twice daily, were given routinely to patients receiving 90 mg/m^2 of doxorubicin, but only after an episode of febrile neutropenia for other patients. Patients randomly assigned to paclitaxel received 175 mg/m^2. Most patients (94%) whose tumor expressed either an estrogen receptor or progesterone receptor received tamoxifen with a recommended duration of 5 years; 21% of patients with receptor-negative tumors also received tamoxifen.

The National Cancer Institute sponsored this trial and supplied G-CSF, obtained from Amgen Pharmaceuticals (Thousand Oaks, CA), and paclitaxel, obtained from Bristol-Myers Squibb (Princeton, NJ). Subsequent to the completion of the trial, Bristol-Myers Squibb provided a grant to the CALGB for statistical support and to update data for submission to regulatory agencies in the United States and Europe.

Patient Entry and Follow-Up

All patients were evaluated every 3 months during year 1, twice annually for the next 2 years, and annually thereafter. Left ventricular ejection fraction was measured at baseline and again at 5 years. A mammogram and chest x-ray were obtained at entry and then yearly. A bone scan was required before treatment was started, but this requirement was discontinued, consistent with changes in clinical practice, after 2,178 patients had been enrolled.

Complete blood counts were obtained twice weekly, and all toxicities of grade 2 or greater severity were collected on the first 325 patients enrolled onto the trial. Only toxicity of grades 3 or higher was routinely recorded on patients after the Data and Safety Monitoring Board had reviewed toxicity data from the first 325 patients.

Statistical Considerations

The primary end point of this study was duration of disease-free survival. Overall survival and toxicity assessment were secondary end points. Disease-free survival is the interval from study entry to first locoregional recurrence, first distant metastasis, or death as a result of any cause. All patients were observed separately for first local and first distant recurrence, second malignancy, delayed cardiotoxicity, and death.

Patients were randomly assigned at the Statistical Center with equal probability to one of six treatment combinations using a stratified random permuted block design. The number of positive axillary nodes was used as the only stratification factor.

In the primary analysis of disease-free and overall survival, a proportional hazards model was used to assess the main effects of increasing doxorubicin dose (60, 75, and 90 mg/m^2), adding paclitaxel (0, 1 [0 is used in the model if the patient did not receive paclitaxel, and 1 is used if the patient did receive paclitaxel]), and the interaction between doxorubicin dose and paclitaxel. Protocol-specified covariates were the number of positive lymph nodes, tumor size, and age. Hazard ratios were obtained from proportional hazards models. Overall hazard ratios were obtained from proportional hazards models. Hazard ratios by year were estimated as the ratio between two groups of the proportion failures observed in time intervals of 1 year in length.

The study was not powered to evaluate effects in subsets. No adjustments in *P* values have been made for multiple comparisons.

An independent Data and Safety Monitoring Board monitored the study. The protocol used an O'Brien-Fleming rule for early stopping but did not specify rules for reporting results. The original protocol called for analyses after 450, 900, 1,350, and 1,800 events. After the 450th event analysis, the Data and Safety Monitoring Board concluded that patients should be aware of the possible benefits from adding paclitaxel and recommended that the results be released; as a result, the study was first presented at the annual meeting of the American Society of Clinical Oncology in May 1998. This decision was also based on a Bayesian predictive analysis using 1,000 simulations.[12] At the time of the 450th event analysis, all patients had been accrued to the study, and every patient had been observed for at least 1 year after random assignment and 6 months after the completion of their protocol-assigned chemotherapy. None of the patients in the trial who were assigned to receive AC only were crossed over to receive paclitaxel subsequent to the results being announced. Bristol-Myers Squibb requested permission to submit the data to the Food and Drug Association (FDA) in support of using paclitaxel as adjuvant treatment for early breast cancer, and in turn, the FDA asked the CALGB to update the database and perform an unplanned analysis after 600 events. An analysis with a median follow-up of 51 months and 900 events was presented to the National Institutes of Health Consensus Conference on Early Breast Cancer in November 2000, and this was the analysis initially submitted to the *Journal of Clinical Oncology* in February 2002. An updated analysis was undertaken in May 2002 and presented at the 2002 American Society of Clinical Oncology meeting. After discussions with the editors of the *Journal of Clinical Oncology*, it was decided that the published article should be based on the most up-to-date results, which have a median follow-up of 69 months; this is the analysis reported here. As part of the quality assurance programs of the cooperative groups, randomly chosen patients' charts were audited on site at least once every 3 years.

RESULTS

Between May 1994 and April 1999, 3,121 patients were randomly assigned and began treatment. In the analyses reported here, all of these patients are included in the treatment group to which they were randomly assigned. Median follow-up is 69 months, and three quarters of the patients have been observed for at least 5 years. The characteristics of the patients enrolled are listed in Table 1. There were no significant imbalances in the randomization.

Table 1. Patient Characteristics by Treatment Arm

Patient Characteristics	All Patients	Treatment Arm				
		Doxorubicin Dose			CA Alone	CA + Paclitaxel
		60 mg/m^2	75 mg/m^2	90 mg/m^2		
No. of patients						
Randomized	3,170	1,060	1,053	1,057	1,580	1,590
Available for analysis*	3,121	1,048	1,040	1,033	1,551	1,570
Median follow-up, months	69	68	69	69	69	69
Age, %						
< 40 years	20	20	22	20	21	20
40-49 years	40	40	39	41	39	41
50-59 years	27	26	28	26	28	26
60+ years	13	13	11	13	12	13
Race, %						
Black	9	10	9	9	9	10
Other nonwhite	7	7	8	6	8	6
Premenopausal, %	62	61	62	62	62	61
Pathologic tumor size, %						
≤ 2 cm	35	35	36	34	35	35
> 5 cm	13	13	13	13	12	13
Positive lymph nodes, %						
1-3 nodes	46	47	46	46	47	46
4-9 nodes	42	42	42	42	42	42
10+ nodes	12	11	12	12	12	12
Receptor positive, ER or PR, %†	66	68	65	65	66	67
ER positive, %	59	61	58	57	58	60
Primary treatment: mastectomy, %	70	69	70	71	70	69

Abbreviations: ER, estrogen receptor; CA, cyclophosphamide and doxorubicin; PR, progesterone receptor.

*Although 3,170 women were randomized, 49 patients never received any protocol therapy, usually because the patient withdrew consent. Because no information is available on the treatment the canceled patients received, their disease-free survival, or their overall survival, all analyses in this article are based on the remaining 3,121 patients.

†Both ER and PR status is known for all but 33 patients, and the status of at least one receptor is known for all but 15 patients. Two thirds of patients were positive for at least one receptor: ER+/PR+, 49%; ER+/PR−, 10%; ER−/PR+, 7%; and ER−/PR−, 33%.

At the time of this analysis, there were 1,054 recurrences (either disease recurrence or death without recurrence) and 742 deaths. There were 343 local recurrences (either isolated or with distant recurrence) and 642 distant recurrences without a local recurrence. Sixty-nine patients died without recurrence.

Efficacy: Doxorubicin Dose

There was no significant reduction in either the hazard of recurrence or death related to doxorubicin dose (Tables 2 and 3). At 5 years, the disease-free survival was 69%, 66%, and 67% for patients randomly assigned to 60, 75, and 90 mg/m^2, respectively. Overall survival for these three treatment groups at the same time point was 79%, 79%, and 77%, respectively (Fig 2). The effects of dose are identical, whether all 3,121 patients are included in the analysis or whether only those treated with CA alone or those treated with CA followed by paclitaxel are included (data not shown).

Table 2. Recurrences and Deaths by Treatment Arm

Variable	No. of Patients Randomized	No. of Patients With a Recurrence	No. of Patients Dead
Doxorubicin dose			
60 mg/m^2	1,060	340	241
75 mg/m^2	1,053	360	241
90 mg/m^2	1,057	354	260
Paclitaxel *v* no paclitaxel			
No paclitaxel	1,580	563	400
Paclitaxel	1,590	491	342

Addition of Paclitaxel

Adding paclitaxel to the CA combination led to hazard reductions of 17% for recurrence (adjusted Wald χ^2 $P = .0023$) and 18% for death ($P = .0064$; Table 3). The 1-year probability of recurrence was 7.9% for CA and 4.6% for CA plus paclitaxel, for a relative reduction of 42% attributable to the addition of paclitaxel. This was seen in the first analysis of this study (median follow-up, 21 months) and has not changed significantly with longer follow-up. These early effects are reflected in the Wilcoxon tests for significance ($P = .0011$ for recurrence and $P = .0098$ for death). At 5 years, 65% of the patients randomly assigned to CA and 70% assigned to CA plus paclitaxel were alive and free of recurrence, whereas 77% and 80%, respectively, were alive (Fig 3).

There was no interaction between doxorubicin dose and the addition of paclitaxel. The addition of a paclitaxel by doxorubicin interaction term to the proportional hazards model did not add predictive information for recurrence ($P = .18$) or death ($P = .20$). Each paclitaxel arm performed better than the corresponding CA arm without paclitaxel.

This study was not powered to assess outcomes in patient subsets, but a limited number of subset analyses were performed. In subsets defined by tumor size, number of positive lymph nodes, and patient age, the only covariates specifically men-

Table 3. Hazard Ratios for Recurrence and Death (from proportional hazard models)

Variable	Hazard Ratio	95% Confidence Interval	*P* Unadjusted* Wilcoxon	*P* Unadjusted* Log-Rank	*P* Adjusted† Wald χ^2
Recurrence					
Doxorubicin dose			.68	.66	.60
60 *v* 90 mg/m^2	0.97	0.84 to 1.13			
60 *v* 75 mg/m^2	0.99	0.91 to 1.06			
Paclitaxel *v* no paclitaxel	0.83	0.73 to 0.94	.0011	.0013	.0023
Death					
Doxorubicin dose			.33	.42	.31
60 *v* 90 mg/m^2	0.91	0.76 to 1.09			
60 *v* 75 mg/m^2	0.96	0.87 to 1.05			
Paclitaxel *v* no paclitaxel	0.82	0.71 to 0.95	.0098	.0061	.0064

*The protocol specifies the Wald χ^2 obtained from the proportional hazards modeling to assess statistical significance for the primary end points. Other tests that give emphasis to earlier (Wilcoxon) or later (log-rank) parts of the time distributions are also shown.

†From a multivariate proportional hazards regression model based on 3,104 patients for whom there are complete data for all the variables used in the model. Pretreatment variables in the model were the square root transformation of the number of positive nodes, the square root transformation of tumor size, and age at study entry. The number of positive nodes and tumor size significantly correlated with both disease-free and overall survival, and age correlated weakly with disease-free survival. *P* values for dose are based on the linear trend.

tioned in the protocol, the addition of paclitaxel was consistently beneficial. Although the magnitude of benefit varied, there was no evidence that adding paclitaxel was significantly better for one of these subsets compared with the others. In unplanned subset analyses, two patient subsets showed particular benefit from paclitaxel: patients with negative or unknown tumor receptor status (hazard ratio = 0.72), and patients who did not receive tamoxifen (hazard ratio = 0.69; Table 4). However, the differences between the effects in these subsets were no longer significant after adjusting for multiple comparisons.

Toxicity

Most patients (98%) who began CA treatment completed all four cycles of therapy, but dose reductions and delays in the initiation of a treatment cycle were significantly more frequent at the higher doxorubicin doses ($P < .0001$). Severe neutropenia, thrombocytopenia, anemia, blood or platelet transfusions, and hospitalizations increased in frequency with each doxorubicin dose escalation ($P < .0001$, linear trend in doxorubicin dose). Patients randomly assigned to either of the higher levels of doxorubicin dose were more prone to develop infection than those treated with 60 mg/m^2 doxorubicin. Patients randomly assigned to 90 mg/m^2 doxorubicin, all of whom routinely received both G-CSF and a prophylactic antibiotic, had about the same frequency of serious infection as those randomly assigned to 75 mg/m^2 doxorubicin, who received G-CSF only as needed. Patients on the highest dose had slightly more nausea and vomiting than those on the lower doses, but stomatitis of grade 2, 3, or 4 was dose related (43%, 30%, and 10% of patients randomly assigned to 90, 75, or 60 mg/m^2 doxorubicin, respectively; $P < .00001$, linear trend).

Fifty-eight patients randomly assigned to receive paclitaxel did not receive any; the most common reason was withdrawal of consent (41 of 58 patients). However, 92% of the patients who started paclitaxel completed all four cycles. Paclitaxel treatment resulted in substantially less hematologic toxicity than CA. The percentage of patients with at least one episode of granulocytopenia ($\leq 500/\mu L$) while receiving CA with a doxorubicin dose of 60 mg/m^2 was 62%, compared with only 16% during paclitaxel therapy. The incidence of infection requiring an antibiotic was less strikingly different (17% of patients receiving 60 mg/m^2 of doxorubicin and 11% of patients receiving paclitaxel). Ten percent of patients on the lowest dose of CA were hospitalized at least once for toxicity, compared with 3% of patients treated with paclitaxel.

Most nonhematologic toxicities were also seen more often and were more severe during treatment with CA than with paclitaxel, including grade II, III, or IV nausea (32% for those receiving the lowest dose of CA *v* 3% during paclitaxel), vomiting (27% *v* 1%), and stomatitis (10% *v* 1%). Hypersensitivity reactions of any severity were seen in 6% of patients during paclitaxel. All but four of these reactions consisted of either urticaria, fever more than 38°C, serum sickness, and/or bronchospasm. Three patients had anaphylaxis, and one patient died of a hypersensitivity reaction. During paclitaxel treatment, 15% of patients had moderate paresthesias, but only 3% had sensory neurotoxicity that interfered with normal functioning. One patient developed a permanent paralysis after one dose of paclitaxel.

Clinically important cardiac dysrhythmias, congestive heart failure, changes in left ventricular ejection fraction, or any other heart symptoms regardless of any possible relationship to treatment occurred in up to 2% of patients during treatment. The incidence of cardiotoxicity during treatment was not significantly different among patients treated with different doxorubicin doses. During posttreatment follow-up, all degrees of cardiotoxicity occurred more often among those randomly assigned to the highest dose of doxorubicin (16%) compared with those treated with 60 (11%) and 75 mg/m^2 of doxorubicin (13%; $P = .0032$, linear trend in doxorubicin dose). There was no difference in incidence of cardiotoxicity between those who did and those who did not receive paclitaxel. Congestive heart failure was observed during active protocol therapy in four (< 1%) and six (< 1%) patients and during

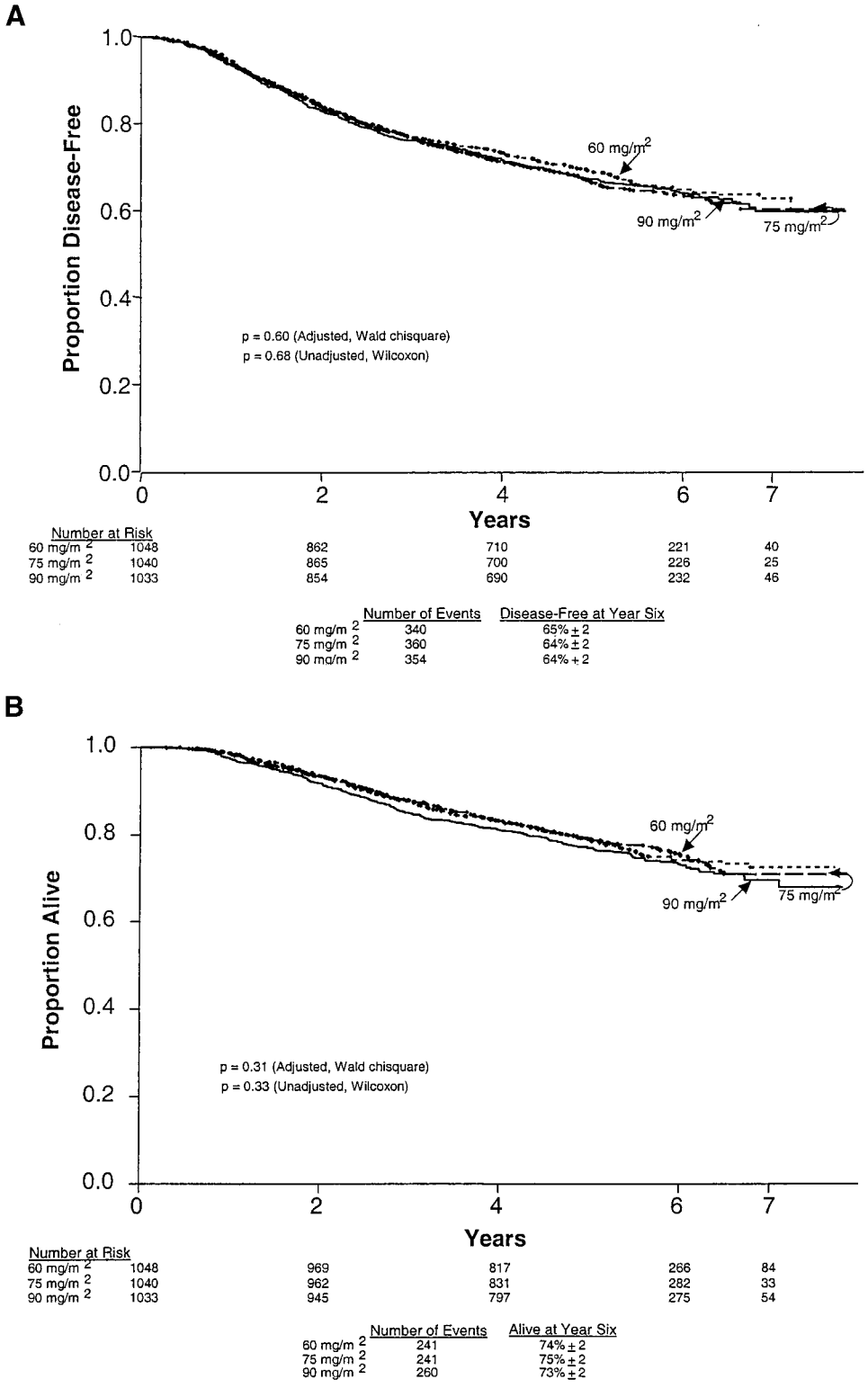

Fig 2. (A) Disease-free and (B) overall survival of patients randomly assigned to doxorubicin doses of 60, 75, or 90 mg/m^2. Adjusted *P* values from multivariate proportional hazards model, unadjusted *P* values from the Wilcoxon test (Table 3), total number of events, number of patients at risk by year of follow-up, and percentage disease free/alive (± SE) at 6 years are shown.

posttreatment follow-up in 23 (1%) and 27 (2%) patients randomly assigned to CA alone and CA plus paclitaxel, respectively.

There were no significant differences in the incidences of secondary malignancies, including leukemias and myelodysplasias, on any of the study arms. On the CA-only arms, there were six cases of acute myeloid leukemia, two cases of myelodysplastic disease, and one case of acute lymphoid leukemia. On the AC plus paclitaxel arm, there were four cases of acute myeloid leukemia, four cases of myelodysplastic disease, and no cases of acute lymphoid leukemia.

Three deaths occurred during treatment. A 74-year-old woman died of respiratory and cardiac failure 1 month after her first cycle of CA with doxorubicin 90 mg/m^2. Two deaths occurred while patients were receiving paclitaxel. A 49-year-old patient

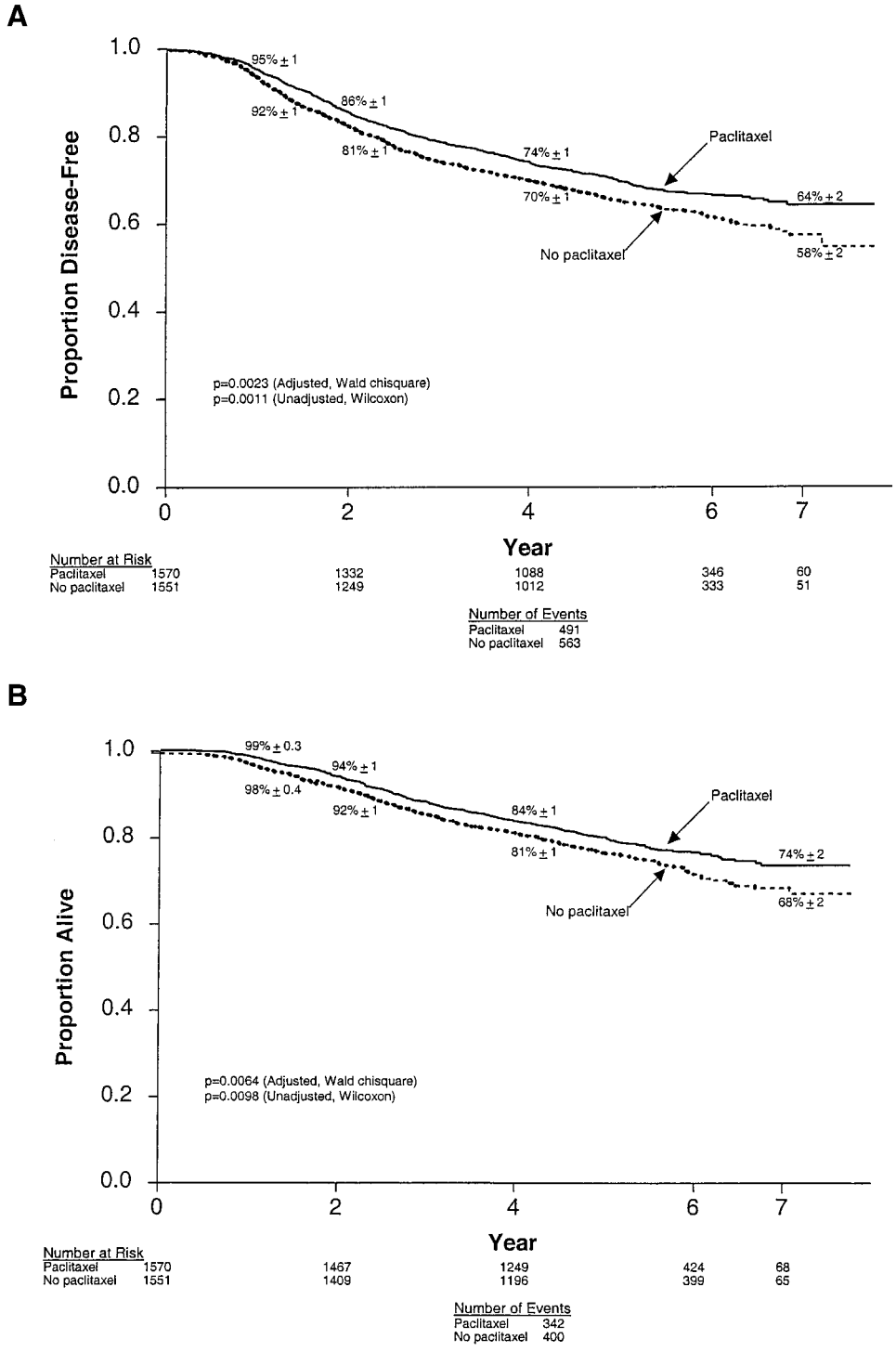

Fig 3. Disease-free (A) and overall survival (B) of patients randomly assigned to cyclophosphamide and doxorubicin alone or with paclitaxel. Adjusted *P* values from multivariate proportional hazards model, unadjusted *P* values from the Wilcoxon test (Table 3), total number of events, number of patients at risk, and percentage disease free/alive (± SE) by year of follow-up are shown.

died of a brain infarction 16 days after her third cycle of paclitaxel. The other patient was 74 years old and had an anaphylactic reaction after a paclitaxel infusion of 13 mL during her second cycle.

DISCUSSION

Escalation of doxorubicin dose in this trial did not improve either the disease-free or overall survival of patients with stage II breast cancer. However, doxorubicin dose escalation substantially increased hematologic toxicity and stomatitis. There was also a significant monotonic increase in long-term cardiotoxicity by doxorubicin dose.

In contrast, compared with the nonpaclitaxel arms, the paclitaxel arms had a decrease in the hazard of recurrence by 17% (hazard ratio = 0.83, adjusted Wald χ^2 P = .0023) and the hazard of death by 18% (hazard ratio = 0.82, adjusted P = .0064). Hazard reductions seen in years 1 and 2 were significant and have remained so with longer follow-up (this is reflected in the unadjusted Wilcoxon P = .0011 and P = .0098, respectively, for these two end points). The reductions in the hazard of

Table 4. Hazard of Recurrence in Patient Subsets Defined by Receptor Status and Use of Tamoxifen: An Unplanned Subset Analysis

Subset*	No. of Recurrences	% of Recurrences†	Hazard Ratio: CA *v* CA+ Paclitaxel	95% Confidence Interval
Receptor positive‡	600	29	0.91	0.78 to 1.07
Receptor negative/unknown	454	43	0.72	0.59 to 0.86
Received tamoxifen§	644	30	0.92	0.79 to 1.08
Received no tamoxifen	403	43	0.69	0.57 to 0.84

*Based on patients with available data.
†Percent of all patients in this subset that have recurred.
‡Estrogen receptor and/or progesterone receptor.
§Without regard to receptor status.
Abbreviation: CA, cyclophosphamide and doxorubicin.

recurrence during year 1 were 41.9%, 41.1%, and 37.4% for the analyses performed after 450, 600, and 900 events. The reductions in hazards during year 2 were 10.7%, 13.6%, and 10.7% for these three analyses, respectively. The absolute difference in 1-year disease-free survival and overall survival between the CA and CA plus paclitaxel arms was 3% and 1%, respectively; the paclitaxel arms had the advantage. An improvement of 5% in disease-free and 3% in overall survival is now evident at 5 years. The benefits from adding paclitaxel to CA observed during the first 5 years should not change at subsequent analyses because 75% of the patients have at least 5 years of follow-up. Whether similar benefits will be observed at longer follow-up intervals (eg, 10 years) cannot be predicted now. The size of the effect from adding paclitaxel to CA is similar to the effect seen from using an anthracycline-containing regimen compared with CMF.[1]

In subsets defined by nodal status, tumor size, and patient age, the addition of paclitaxel to CA consistently proved advantageous. However, the effect was largest among those whose tumors were hormone-receptor negative and among those who received no adjuvant tamoxifen compared with all other patient subgroups. As these were unplanned subset analyses and not anticipated outcomes, these observations must be interpreted cautiously. Because patients with receptor-positive tumors relapse later than those with receptor-negative tumors, differences in the effectiveness of treatment may diminish with longer follow-up. It would be premature to conclude that these differences in subsets defined by receptor status or tamoxifen use are limited to paclitaxel and not other chemotherapeutic agents. In recent overviews, the benefits from adjuvant chemotherapy were generally smaller in patients with receptor-positive tumors and among those who had received adjuvant tamoxifen.[1,13] Few studies in patients with early breast cancer have focused on either receptor status or tamoxifen use as predictive factors for response to adjuvant chemotherapy, but this subset analysis indicates that this should be prospectively evaluated in future trials.

The CA and CA plus paclitaxel arms differed both in duration of therapy (3 *v* 6 months) and in the drugs used. From this study alone, we cannot determine the individual contribution of each of these factors to the observed outcomes. Three months of CA is standard treatment in the United States because most randomized studies have not shown a clear advantage for longer durations of therapy, and longer durations are associated with an increased likelihood of cardiotoxicity.[1,14] However, there are still insufficient data to rule out the possibility that treatment duration is important. An overview of all randomized trials designed to evaluate the importance of treatment duration demonstrated a reduction ± SD of 7% ± 4% ($P = .06$) in the annual odds of recurrence favoring longer over shorter treatment but no reduction in the annual odds of death.[1] Most of the studies in this overview compared treatment durations longer than 6 months. However, in one study that has been recently updated, [15] 621 premenopausal women with nodal involvement were randomly assigned to either three or six cycles of fluorouracil, epirubicin, and cyclophosphamide.[1,15] A significant disease-free and overall survival advantage has emerged for patients receiving the longer treatment duration.

Another potential confounding factor is the possibility that the dose effect was compromised because the higher doses of doxorubicin were administered over 2 days. This seems unlikely because continuous infusions of doxorubicin over 48 to 96 hours seem to be as effective as bolus infusions in patients with metastatic disease,[16] but there are no direct comparisons of administering the same dose of doxorubicin over 2 days rather than as a single bolus dose. On the basis of the known pharmacokinetics of doxorubicin, the area under the curve should be the same whether the dose is administered over 1 day or in divided doses.

The original protocol for this study called for a final analysis 4 years after the end of patient accrual. This occurred in April 2001. Times for analyses up to that point were defined by the numbers of events, and the data safety monitoring board used these time points as a guide in announcing the results of the trial. The data safety monitoring board released the results after the first of these analyses, which occurred after 450 events. There have been two updates of the results since that time. The first was in response to a request from the FDA; the time point for this analysis was not data derived. Because of the size of the trial, the importance of the questions for clinical practice in the United States, and the interest in this trial by the oncology community, a fourth analysis was undertaken. This is the analysis reported here. Although there are several widely accepted approaches to making adjustments in statistical significance for multiple analyses taken to determine whether a trial should be stopped early, there is no similar standard for adjusting statistical inference for analyses taken to determine the time for reporting results, and no adjustments have been made.

This is the third large, multicenter, randomized trial that has failed to demonstrate any advantage to breast cancer patients from moderate dose escalation of either cyclophosphamide or doxorubicin with hematopoietic growth factor support for periods of 3 to 4 months.[9,10] More extreme dose escalation with stem cell support has similarly failed to improve survival substantially or significantly.[17-21] Dose escalation may benefit some breast cancer patients, such as those whose tumors overexpress HER2/*neu*.[22,23] This hypothesis was addressed in this study and will be reported at a later date. At this time, however, there are no data from randomized trials to justify dose escalation of cyclophosphamide beyond 400 mg/m^2 and doxorubicin beyond 40 mg/m^2.[7-10]

In this study, the administration of a non–cross-resistant drug, paclitaxel, as a single agent after completion of treatment with a standard therapy, CA, improved disease-free and overall survival. In another study,[24] 174 patients were randomly assigned to either eight cycles of CA plus fluorouracil or to four cycles of paclitaxel followed by four cycles of CA plus fluorouracil. After a median follow-up of 44 months, there was a 26% reduction in the number of recurrences and a 4% difference in disease-free survival, favoring those treated with paclitaxel, but these differences failed to reach statistical significance in this small study. These two studies taken together still do not rule out the possibility that eight cycles of CA might be as effective as the sequence described here. However, eight cycles of CA using conventional-dose schedules would be considerably more toxic, with unacceptable levels of cardiomyopathy.[15] For this reason, we conclude that the use of four cycles of CA followed by four cycles of paclitaxel is a reasonable treatment choice for at least some patients with early breast cancer.

APPENDIX

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