Phase III Trial of Doxorubicin, Paclitaxel, and the Combination of Doxorubicin and Paclitaxel as Front-Line Chemotherapy for Metastatic Breast Cancer: An Intergroup Trial (E1193)

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Purpose: **Between February 1993 and September 1995, 739 patients with metastatic breast cancer were entered on an Intergroup trial (E1193) comparing doxorubicin (60 mg/m^2), paclitaxel (175 mg/m^2/24 h), and the combination of doxorubicin and paclitaxel (AT, 50 mg/m^2 and 150 mg/m^2/24 h, plus granulocyte colony-stimulating factor 5 mg/kg) as first-line therapy. Patients receiving single-agent doxorubicin or paclitaxel were crossed over to the other agent at time of progression.**

Patients and Methods: **Patients were well balanced for on-study characteristics.**

Results: **Responses (complete response and partial response) were seen in 36% of doxorubicin, 34% of paclitaxel, and 47% of AT patients (P = .84 for doxorubicin *v* paclitaxel, P = .007 for *v* AT, P = .004 for paclitaxel *v* AT). Median time to treatment failure (TTF) is 5.8, 6.0, and 8.0 months for doxorubicin, paclitaxel, and AT, respectively (P = .68 for doxorubicin *v* paclitaxel, P = .003 for doxorubicin *v* AT, P = .009 for paclitaxel *v* AT). Median survivals are 18.9 months for patients taking doxorubicin, 22.2 months for patients taking paclitaxel, and 22.0 months for patients taking AT (P = not significant). Responses were seen in 20% of patients crossing from doxorubicin → paclitaxel and 22% of patients crossing from paclitaxel → doxorubicin (P = not significant). Changes in global quality-of-life measurements from on-study to week 16 were similar in all three groups.**

Conclusion: **(1) doxorubicin and paclitaxel, in the doses used here, have equivalent activity; (2) the combination of AT results in superior overall response rates and time to TTF; and (3) despite these results, combination therapy with AT did not improve either survival or quality of life compared to sequential single-agent therapy.**

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DESPITE MORE than three decades of research with combination chemotherapy, the great majority of patients with metastatic breast cancer continue to die from their disease. Although responses to front-line chemotherapy regimens are common, median durations of response are generally short, and long-term disease-free survivors are few, indicating a continuing need for novel therapies.

In 1991, Holmes et al[1] reported that the chemotherapeutic agent paclitaxel induced objective remissions in 56% of patients with metastatic breast cancer, a finding rapidly confirmed by Reichman et al.[2] Interest in this agent was derived not only from its activity, but also from its novel mechanism of action. Paclitaxel shifts the dynamic equilibrium in microtubule assembly from tubulin to microtubules, resulting in microtubules that are excessively stable and therefore dysfunctional.[3]

A common assumption underlying therapy for metastatic breast cancer has been that combining agents will result in regimens with superior response rates, as well as improved palliative efficacy, disease-free survival, and overall survival. Before the advent of paclitaxel, the chemotherapeutic agent commonly thought to have the greatest single-agent activity was the antitumor antibiotic doxorubicin. Reasoning that the combination of doxorubicin with paclitaxel would result in superior therapeutic activity, we compared single-agent doxorubicin, single-agent paclitaxel, and the combination of doxorubicin and paclitaxel (AT) as front-line therapy for patients with metastatic breast cancer.

PATIENTS AND METHODS

Patients were considered eligible if they had histologically confirmed breast adenocarcinoma with progressing regional or metastatic disease. Patients may have received prior nonanthracycline, nontaxane adjuvant chemotherapy, as long as adjuvant chemotherapy had ceased ≥ 6 months previously. Patients may have received prior hormonal therapy in either the metastatic or adjuvant setting.

Patients must have had measurable and or evaluable disease, as determined by standard Eastern Cooperative Oncology Group (ECOG) criteria. Cytologically positive pleural or peritoneal effusions were considered evaluable disease provided local intracavitary treatment had not been administered. Pleural effusions may not have been previously drained. Blastic and mixed blastic-lytic osseous metastases were evaluable provided either an analgesic requirement or a decrease in performance status accompanied them.

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Table 1. Patient Characteristics

	A (n = 224)		T (n = 229)		A + T (n = 230)	
	No.	%	No.	%	No.	%
Race						
White	178	79	183	80	179	78
Black	35	16	33	14	33	14
Hispanic	9	4	8	4	11	5
Other	2	1	5	2	7	3
Age						
Median	58		56		56	
Range	25 to 79		27 to 76		27 to 78	
ER status						
Negative	56	25	63	27	61	26
Positive	102	46	107	47	101	44
Unknown	66	29	59	26	68	30
Any disease-free interval (from checklist)						
No	80	36	72	31	72	31
Yes	140	62	150	66	151	66
Unknown	4	2	7	3	7	3
Dominant site of disease						
Soft tissue	41	18	30	13	44	19
Osseous	47	21	38	17	45	20
Visceral	136	61	161	70	141	61
Number of sites						
One	54	24	58	25	61	26
Two	52	23	50	22	62	27
Three or more	118	53	121	53	107	47
Day 1 PS						
0	93	42	94	41	97	42
1	97	43	91	40	91	40
2	23	10	27	12	20	9
3	0		0		1	0
Unknown	11	5	17	7	21	9
Prior systemic therapy						
None	96	43	91	40	93	40
Adjuvant only	64	29	69	30	71	31
Advanced only	30	13	35	15	32	14
Both	34	15	33	14	34	15
Unknown	0		1	0	0	
Adjuvant chemotherapy						
No	155	69	157	69	155	67
Yes	69	31	72	31	75	33
Adjuvant hormones						
No	155	69	165	72	172	75
Yes	69	31	64	28	58	25
Metastatic hormones						
No	160	71	156	68	158	69
Yes	64	29	73	32	72	31
Disease-free interval (calculated)						
None less than 1 month	77	34	65	28	68	30
1-12 months	13	6	22	10	16	7
12-24 months	29	13	35	15	21	9
24-60 months	59	26	57	25	65	28
60-120 months	35	16	36	16	44	19
More than 120 months	11	5	14	6	16	7

NOTE: No statistically significant difference is seen for any of the above patient characteristics.

Abbreviations: A, doxorubicin; T, paclitaxel; ER, estrogen receptor; PS, performance status.

Table 2. Incidence of Moderate and Severe Adverse Effects After Randomization

Adverse Effect	DOX (%)	PAC (%)	DOX + PAC (%)
Leukopenia	49.6	59.9	54.9
Thrombocytopenia	5.4	2.1	16.0
Anemia	6.2	9.5	17.2
Infection	4.1	8.3	12.7
Cardiac complications	8.7	3.7	8.6
Neurologic complications	1.6	3.7	10.7
Vomiting	6.6	2.5	4.5
Diarrhea	1.6	1.6	4.5
Stomatitis	7.8	2.9	4.5
Lethal toxicity	2.5	1.6	1.6

NOTE: The common toxicity criteria of the National Cancer Institute were used to define moderate (grade 3), average (grade 4), or lethal (grade 5) toxicity.

Abbreviations: DOX, doxorubicin; PAC, paclitaxel.

Patients were required to have adequate renal, hematologic, and hepatocellular function, an ECOG performance status of 0, 1, or 2, and a life expectancy of ≥ 3 months. At least 4 weeks must have elapsed since major surgery. Patients with a history of congestive heart failure, a myocardial infarction within 6 months, or ischemic heart disease requiring medication were ineligible, as were patients with cardiac conduction abnormalities and patients receiving agents known to alter cardiac conduction. Patients with a history of deep venous thrombophlebitis, pulmonary thromboembolism, or other thromboembolic condition were ineligible. Pregnant patients were ineligible.

Initially, patients must have had no prior radiotherapy, with the exception of breast or chest wall radiation. A later amendment allowed for radiation to less than 25% of marrow containing bone. Patients with a prior malignancy within 5 years were ineligible, with the exception of curatively treated nonmelanoma skin cancer or carcinoma-in situ of the cervix.

Patients were randomized to receive either doxorubicin 60 mg/m^2 intravenously, paclitaxel 175 mg/m^2 over 24 hours, or the combination of doxorubicin 50 mg/m^2 followed 3 hours later by paclitaxel 150 mg/m^2 over 24 hours. Therapy was administered every 3 weeks. Doxorubicin was administered for a maximum of eight cycles; paclitaxel was administered until disease progression. At time of progression, patients were crossed over from doxorubicin $\rightarrow$ paclitaxel or from paclitaxel $\rightarrow$ doxorubicin.

This trial was designed to detect an improvement of 15% in the overall response rate (complete response [CR] plus partial response [PR]) between any two treatment arms, and to detect an improvement of 50% in time to treatment failure (TTF) in any pair-wise comparison. Single-agent doxorubicin was expected to have a response rate of 30% to 35%, and a median TTF of 6 to 8 months. The Bonferroni correction was used to adjust for multiple comparisons within each primary end point. With 220 eligible patients on each arm, the trial had a power of 0.84 to detect a 15% increase in response rate from 35% to 50%, and 95% power to detect a 50% improvement in TTF from 6 to 9 months, testing at the one-sided .05 significance level with a Bonferroni correction. Two-sided *P* values are reported in this article.

Overall survival was measured from date of study entry to death or date when the patient was last known to be alive. TTF was measured from date of study entry to date of progressive disease, toxic death, or death attributed to breast cancer within 6 weeks of the date the patient was last known to be alive with stable disease. In the presence of disease progression that did not meet ECOG criteria, date of crossover entry was taken as date of progression; if progression could not be confirmed at crossover entry, the patient was censored at that time. Patients last known to be in response or stable were censored at that time. Patients not evaluable for response were censored at study entry unless date of progression could be determined.

Response rates were compared using the Fisher's exact test. Severity of toxicity was compared using the Kruskal-Wallis test for ordered data. TTF and overall survival were compared using the log-rank test. Cox proportional hazards multiple regression models were explored to assess the relative effect of treatment and known prognostic factors on TTF and overall survival.

Quality of life was assessed during induction therapy using the Functional Assessment of Cancer Therapy—Breast (FACT-B), administered at baseline and at week 16. Data were analyzed using *t*-tests and analysis of variance.

RESULTS

Between February of 1993 and September of 1995, a total of 739 patients were randomized. Eight of these patients have been

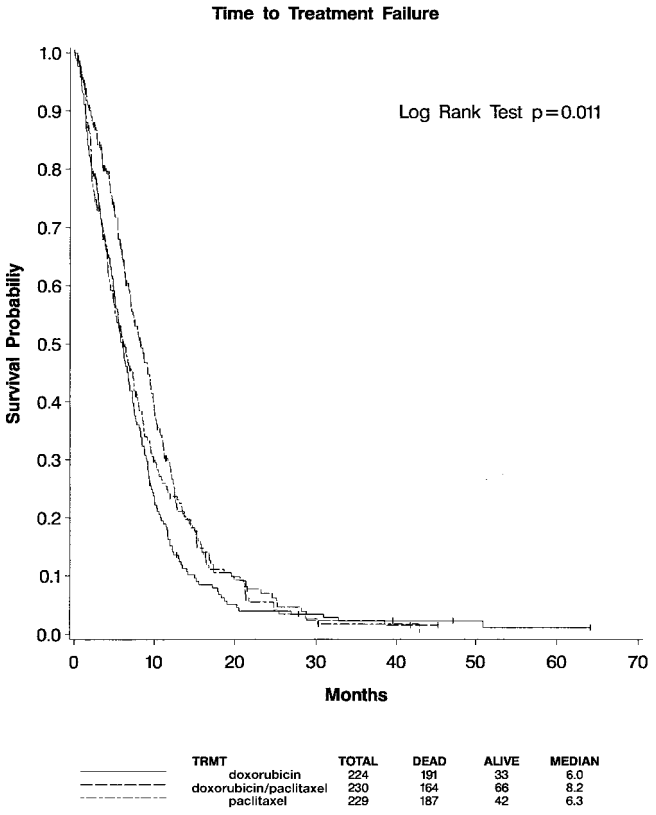

Fig 1. Time to treatment failure.

canceled: three patients were duplicate registrations, three patients became ineligible before treatment began, one patient was delayed for radiotherapy to bone metastases, and one patient for physician preference. Of the remaining 731 patients, 245 were randomly assigned to doxorubicin, 242 were randomly assigned to paclitaxel, and 244 were randomly assigned to AT. Thirty-three patients have been excluded from analysis for reasons of ineligibility. These reasons include concurrent tamoxifen (two patients), no evaluable disease (seven patients), adjuvant chemotherapy within 6 months (one patient), no histologic proof of breast cancer (one patient), hormonal therapy within 2 weeks (eight patients), prior metastatic breast cancer (four patients), less than 4 weeks since major surgery (one patient), laboratory values more than 2 weeks old (two patients), cardiac history (one patient), consent signed after randomization (one patient), inadequate on-study evaluation (four patients), and extensive prior radiation (one patient).

Included in this analysis are 14 patients who had received radiation before study entry who were initially deemed ineligible because of inadvertent narrow phrasing of radiation criteria (which initially excluded radiation therapy to any site other than chest wall, but was later amended to allow radiation involving < 25% of marrow-containing bone), as well as 30 patients initially deemed ineligible because they were receiving drugs known to alter cardiac conduction (generally beta-blockers). The latter were included after analysis revealed no increased cardiac toxicity compared with other patients entered into the trial.

Patient characteristics are shown in Table 1. All three arms were well matched for race, age, estrogen receptor (ER) status, disease-free interval, dominant site of disease, number of sites of disease, performance status, and prior systemic therapy.

Toxicity data are shown in Table 2 for patients receiving their initial chemotherapy regimen. Lethal toxicities were rare in all groups. Although grade 4 neutropenia was most common in patients receiving paclitaxel, grade 4 or 5 infection or neutropenic fever were less common than in patients receiving combination AT therapy; paclitaxel-induced neutropenia was profound but of brief duration. Cardiac toxicity was equivalent in patients receiving single-agent doxorubicin and combination AT therapy.

Objective responses were seen in 36% of patients receiving doxorubicin, 34% of patients receiving paclitaxel, and 47% of patients receiving combination AT therapy ($P = .77$ for doxorubicin *v* paclitaxel, .017 for doxorubicin *v* AT, and .006 for paclitaxel versus AT). The CR rate for all three arms was disappointing: 6% for those taking doxorubicin, 3% for those taking paclitaxel, and 9% for those taking AT (a nonsignificant difference after adjustment for multiple comparisons). Similarly, median TTF (Fig 1) was longer for AT (8.2 months) than for either single-agent doxorubicin (6.0 months) or single-agent paclitaxel (6.3 months) ($P = .0022$ for doxorubicin *v* AT, and .0567 for paclitaxel *v* AT).

Despite the statistically significant improvements in response rate and TTF for combination as opposed to single-agent therapy, there was no significant difference in overall survival, with median survivals of 19.1 (arm A), 22.5 (arm B), and 22.4 months (arm C) ($P = .60$ for arm A *v* B, $P = .82$ for arm A *v* C; $P = .49$ for arm B *v* C). Figure 2 demonstrates the absence of any trend favoring combination therapy. In multivariate analysis (Table 3), using the Cox proportional hazards model, ER negativity, the presence of three or more sites of disease, a short disease-free interval (1 to 24 months), and prior systemic therapy all predicted for impaired overall survival. Treatment regimen was not a significant predictor of survival.

Patients receiving single-agent doxorubicin and single-agent paclitaxel were scheduled by protocol to cross-over to the other single agent at time of disease progression, allowing for an analysis of cross-over response and relative resistance to therapy. Responses were seen in 28 of 129 (22%) of patients crossed over to paclitaxel and in 25 of 128 (20%) of patients crossed to doxorubicin. The median TTF for patients taking cross-over paclitaxel was 4.5 months; the median TTF for patients taking cross-over doxorubicin was 4.2 months. Median survival for patients taking paclitaxel after entry to cross-over is 14.9 months, whereas median survival for patients taking doxorubicin is 12.7 months ($P = .11$). If only those patients who relapsed after a response on induction therapy are examined, 12 of 40 patients crossing from doxorubicin to paclitaxel responded, compared to 7 of 38 patients crossing from paclitaxel to doxorubicin ($P =$ not significant).

Quality of life was assessed using the FACT-B scale at two time points during induction therapy. The FACT-B includes five general subscales (physical, social, relationship with physician, emotional, and functional), as well as a breast cancer–specific subscale. Maximum possible score is 148 points; a higher score is indicative of better quality of life. A total of 687 of the 738 patients (93%) randomized completed the baseline survey. This included 640 of the 683 eligible patients (94%).

Among the eligible patients with baseline surveys, 451 patients (70%) completed the follow-up assessment at week 16. Changes in

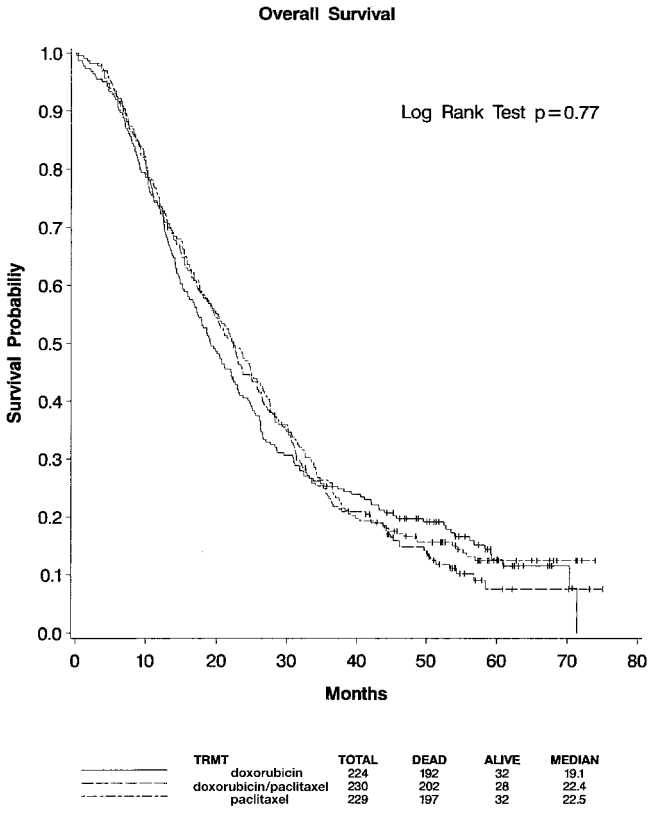

Fig 2. Overall survival.

these scores were compared between the randomized treatment arms, to see if there were significant differences in changes of quality of life. This reflected our hypothesis that there might be substantial differences in quality of life during paclitaxel-containing therapy, even if there were no differences in the objective response rates. Table 4 presents mean FACT-B scores at baseline and week 16, as well as mean change by week 16, by treatment arm. There were no statistically significant differences between the two single-agent arms ($P = .57$), between doxorubicin and the combination AT therapy ($P = .52$), or between paclitaxel and the combination AT therapy ($P = .93$). No statistically significant differences were observed between treatment arms on any of the subscales.

DISCUSSION

For most of the last three decades, combination chemotherapy has represented the standard of care for hormone-refractory metastatic breast cancer. Its use is based on both theoretic principles and practical experience. Theory predicted that the use of non–cross-resistant agents with nonoverlapping toxicities would result in therapeutic synergy, overcoming drug resistance.[4-6]

Table 3. Factors Associated With Overall Survival: Multivariate Analysis

Factor	RR	*P*
ER negative	1.7	.0001
Visceral dominant	1.4	.004
Three or more sites	1.4	.005
1-24 month DFI	1.3	.03
Prior systemic Rx	1.1	.03

Abbreviations: ER, estrogen receptor; DFI, disease-free interval; Rx, therapy; RR, relative risk ratio.

Table 4. Quality of Life of Patients Receiving Induction Chemotherapy

	Doxorubicin (N = 136)	Paclitaxel (N = 150)	Doxorubicin and Paclitaxel (N = 165)
Baseline	107.5	110.3	111.0
16 weeks	105.8	107.4	108.0
Change	−1.7	−2.8	−3.0

Practical experience, beginning with the pioneering work of Greenspan,[7] indicated that combination regimens are associated with higher response rates than single-agent regimens. Randomized trials from the era before taxane indicated that combination chemotherapy was superior to single-agent therapy in the metastatic setting with regard to response rates and/or overall survival,[8-17] a finding confirmed in a recent overview analysis.[18] These trials did not test the hypothesis that combination chemotherapy resulted in therapeutic synergy, in that they did not compare combination therapy with sequential single-agent therapy using the same agents. The few trials comparing combination with sequential therapy in this setting gave conflicting results, although all were statistically underpowered.[19-21]

Trial E1193 tested whether the combination of two active drugs, representing what are arguably the two most active classes of agents (anthracycline and taxanes) used in breast cancer, might prove superior to sequential, single-agent therapy with the same agents. Combination therapy resulted both in a superior overall response rate and a superior TTF, two frequent measures of efficacy in metastatic chemotherapy trials. Despite this superiority, combination therapy failed to improve overall survival. Perhaps more importantly, given the usually fatal nature of the disease, combination therapy did not improve quality of life.

Several reasons may explain these failures. First, patients failing to respond to a single agent may respond to another, so that what might be called the "composite response rate" to therapy (the percentage of patients responding at some point during either their first or second regimen) may approximate the response rate seen with the combination. Second, response rate and TTF may represent poor surrogates for overall survival, which in turn, may be more strongly related to the underlying biology of the disease. In support of this argument, multivariate analysis demonstrates that ER status, number of disease sites, and disease-free interval, rather than chemotherapy type, affected survival. Third, the use of combination therapy often involves compromises with regard to dose and frequency of administration, and these compromises may negate the promise of synergy.

Similarly, the inability of increasing response rate and TTF to improve quality of life may reflect the very loose correlation between such standard markers of therapeutic efficacy and quality of life. Indeed, a combination regimen might impair rather than improve quality of life if it induces toxicity disproportionate to response. Until agents with true therapeutic synergy are discovered, sequential chemotherapy represents a reasonable option for patients with metastatic breast cancer.

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