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ORIGINAL REPORT

Comparison of Doxorubicin and Cyclophosphamide Versus Single-Agent Paclitaxel As Adjuvant Therapy for Breast Cancer in Women With 0 to 3 Positive Axillary Nodes: CALGB 40101 (Alliance)

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See accompanying editorial on page 2284

A B S T R A C T

Purpose
Optimal adjuvant chemotherapy for early-stage breast cancer balances efficacy and toxicity. We sought to determine whether single-agent paclitaxel (T) was inferior to doxorubicin and cyclophosphamide (AC), when each was administered for four or six cycles of therapy, and whether it offered less toxicity.

Patients and Methods
Patients with operable breast cancer with 0 to 3 positive nodes were enrolled onto the study to address the noninferiority of single-agent T to AC, defined as the one-sided 95% upper-bound CI (UCB) of hazard ratio (HR) of T versus AC less than 1.30 for the primary end point of relapse-free survival (RFS). As a 2 × 2 factorial design, duration of therapy was also addressed and was previously reported.

Results
With 3,871 patients enrolled onto the trial, a median follow-up period of 6.1 years, and 437 RFS events, we achieved an HR of 1.26 (one sided 95% UCB, 1.48; favoring AC does not allow a conclusion of noninferiority of T with AC; UCB > 1.3). With 266 patient deaths, the HR for overall survival (OS) was 1.27 favoring AC (UCB, 1.56). The estimated absolute advantage of AC at 5 years is 3% for RFS (91 *v* 88%) and 1% for OS (95 *v* 94%). All nine treatment-related deaths were patients receiving AC and are included in the analyses of both RFS and OS. Hematologic toxicity was more common in patients treated with AC, and neuropathy was more common in patients treated with T.

Conclusion
This trial did not show noninferiority of T to AC, a conclusion that is unlikely to change with additional events and follow-up. T was less toxic than AC.

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INTRODUCTION

A large proportion of patients with breast cancer now show symptoms of early-stage disease and, with modern surgical, radiation, and systemic treatments, their long-term survival rates have continually improved. In the United States, 80% of patients with breast cancer survive 10 years or longer. Adjuvant chemotherapy has played a major role in improving outcomes, and there has been a continual effort to identify regimens with higher relapse-free (RFS) and overall survival (OS) rates.[1] As long-term outcomes have improved and issues of survivorship have gained more attention, short- and long-term toxicity have become increasingly important.

National Surgical Adjuvant Breast and Bowel Project trial B-15 showed that the four cycles of cyclophosphamide and doxorubicin (AC) was equivalent to six cycles of cyclophosphamide, methotrexate, and fluorouracil and established AC as a standard adjuvant regimen for breast cancer.[2] More recently, taxanes have been added to AC regimens or substituted for one of the agents. Some studies have investigated four cycles of therapy while others have used six cycles.[3-7]

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Cancer and Leukemia Group B (CALGB) trial 40101 is a North American Breast Intergroup trial that used a 2 × 2 factorial design to test the noninferiority of single-agent paclitaxel (T) with AC and the superiority of six cycles of therapy over four cycles. Interest in testing the noninferiority of T with AC was based on data from patients with locally advanced or metastatic disease, in which single-agent taxanes seemed to have relatively equivalent efficacy compared with combination chemotherapy built on the AC backbone.[8,9] The decision to test four cycles versus six cycles of therapy was based on the use of four or six cycles in previous studies without evidence to support one duration over the other.[3-7] The results of the duration of therapy question have been previously published and have shown no difference in outcome for six cycles versus four cycles of therapy.[10] Our article outlines the results from the T versus AC component of the study.

PATIENTS AND METHODS

CALGB 40101 (NCT00041119, supported by the National Cancer Institute and CALGB) was initiated in 2002 as a 2 × 2 factorial design to test as adjuvant chemotherapy the noninferiority of T versus AC and the superiority of longer versus shorter therapy, initially for women with node-negative disease and eventually for women with 1 to 3 positive nodes as well. When the protocol was originally written, the comparison was termed "equivalence" and is stated as such in the protocol, but current terminology is "noninferiority" and this term is used in our article.

Eligibility criteria included women older than 18 years old who had operable breast cancer and whose treating physicians deemed they needed adjuvant chemotherapy based on their tumor size, grade, hormone receptor status, HER2/*neu* status, lymphovascular involvement, and potentially other factors. The protocol provided general guidelines for tumor characteristics that might warrant consideration of adjuvant chemotherapy, however, the final decision was left to the treating physician. Protocol guidelines suggested that for patients with node-negative and hormone receptor–positive disease, patients with tumors ≥ 1 cm in size should be considered for chemotherapy; for patients with hormone receptor-negative disease, patients with tumors of any size might be considered for chemotherapy. For patients with 1 to 3 positive nodes, tumors of any size and any hormone receptor status should be considered for chemotherapy. This was intended to replicate community-standard nonprotocol decision-making regarding the need for chemotherapy in these patients. Estrogen receptor (ER), progesterone receptor (PgR) and HER2 testing was performed by the local institution without central review. Patients could not have locally advanced disease, such as skin involvement, chest wall involvement, or inflammatory cancer. Patients were required to have adequate liver, renal, and hematologic function. When the study was activated in 2002, only women with node-negative disease were eligible; in 2005, study eligibility was expanded to include women with one to three positive axillary nodes. The rationale for this modification was two-fold; the protocol-specified regimens were appropriate for this group of patients, and accrual would be increased. Sentinel node assessment was acceptable for patients with negative sentinel nodes. If sentinel node(s) were positive, a completion dissection was required, with at least six total nodes (sentinel nodes plus dissection) required for evaluation. Tumor margins were required to be negative for patients undergoing both breast-conserving surgery and mastectomy.

In February 2008, with a total enrollment of 3,171 patients, the six-cycle study arms were closed because of slowing accrual, and randomization was henceforth restricted to two study arms: four cycles of AC and four cycles of T. The trial was permanently closed to accrual in July 2010 because of continued slowing accrual, with a final total accrual of 3,871 patients, which was short of the planned target of 4,646 patients.

At trial inception, AC was administered once every 3 weeks for four cycles (12 weeks) or six cycles (18 weeks) and T was administered weekly for 12 or 18 weeks (3 weeks of T was equivalent to one cycle). During this initial period of the trial, 571 patients were accrued. In 2003, when CALGB 9741 showed superiority of dose-dense therapy administered every 2 weeks versus every 3 weeks,[11] CALGB 40101 was amended so AC and T were administered every 2 weeks for four or six cycles. AC was administered as doxorubicin 60 mg/m^2 intravenously, and cyclophosphamide as 600 mg/m^2 IV. Paclitaxel was administered as 80 mg/m^2 IV when given weekly, and 175 mg/m^2 intravenously when given once every 2 weeks.. WBC growth factor support (either filgrastim or pegfilgrastim) was recommended for patients receiving dose-dense therapy.

Hormone therapy (tamoxifen for any patient or aromatase inhibitors in postmenopausal women) was recommended for patients with hormone receptor–positive tumors. After 2005, trastuzumab was permitted for women with HER2-positive tumors.

Radiation therapy was required for women undergoing breast-conserving surgery, though the type of radiation (eg, whole breast or partial breast) was determined by the treating physicians. Postmastectomy radiation could be given at the discretion of the treating physicians.

Patients had to have been enrolled and randomly assigned onto the study within 84 days of their last breast surgery, and treatment had to be initiated within 7 days of random assignment. Randomization used a permuted block design with fixed block size of 12 allocated patients with equal probability to one of the four possible treatment arms. Randomization was stratified by menopausal status, hormone receptor status, and, after October 2005, HER2 status.

After completion of protocol chemotherapy, patients were asked to receive follow-up every 6 months for the first 2 years and annually thereafter for 15 years after enrollment.

Primary objectives of the study were to test the noninferiority of T compared with AC and the superiority of six cycles of therapy over four cycles of therapy, both in regard to RFS. Secondary objectives included the same comparisons for OS. Other secondary objectives included the evaluation of toxicities for patients receiving AC and T for six cycles and four cycles of therapy and the induction of menopause (defined as > 12 months without menstruation) in premenopausal women by treatment arm.

Each patient gave written approval on a protocol-specific, institutional review board–approved consent form.

The primary study end point was RFS as defined by STEEP (Standardized Definitions of Efficacy Endpoints) criteria, measured from study entry until local recurrence, distant relapse, or death without relapse, whichever occurred first.[12] All new primary sites, regardless of location, were considered adverse events and not events in RFS. Surviving patients who were relapse-free were censored at the date of last clinical assessment. The secondary end point of OS was measured from study entry until death from any cause; surviving patients were censored at the date of last contact.

The study was designed with 89% power (one-sided alpha, .05) to test the noninferiority of T with AC. Noninferiority was defined as the 5-year RFS of T being not less than 84.7%, assuming a 5-year RFS of 88% for AC. This corresponds to a hazard ratio (HR) of T:AC of 1.3. The study's target accrual was 4,646 patients, with 567 RFS events expected at the final analysis.

The test of noninferiority used an HR of T:AC and the one-sided 95% upper bound CI obtained from a univariable proportional hazards model stratified by the study stratifiers. An upper bound of less than 1.3 was evidence to conclude that T was noninferior to AC.

The primary analysis used proportional hazards modeling that adjusted for tumor size, number of involved lymph nodes, hormone receptor status (either ER- or PgR-positive status *v* -negative), and menopausal status.[13] Except for the agent, the statistical significance of each variable included in the models was assessed using the corresponding Wald χ^2 statistics. HRs and their 95% CIs were obtained from multivariable proportional hazards models. The relationship between agent and treatment length regarding RFS and OS was described with proportional hazards models using an interaction term constructed as the cross-product of the agent and length. To address the impact of modifying treatment duration (from every 3 weeks to every 2 weeks) and nodal involvement (from zero to 0 to 3) on clinical outcome, primary analyses were repeated in an ad hoc manner on the resulting subgroups. Because the study was not powered to assess interactions or subgroup analyses, any such references are considered descriptive and presented without significance levels.

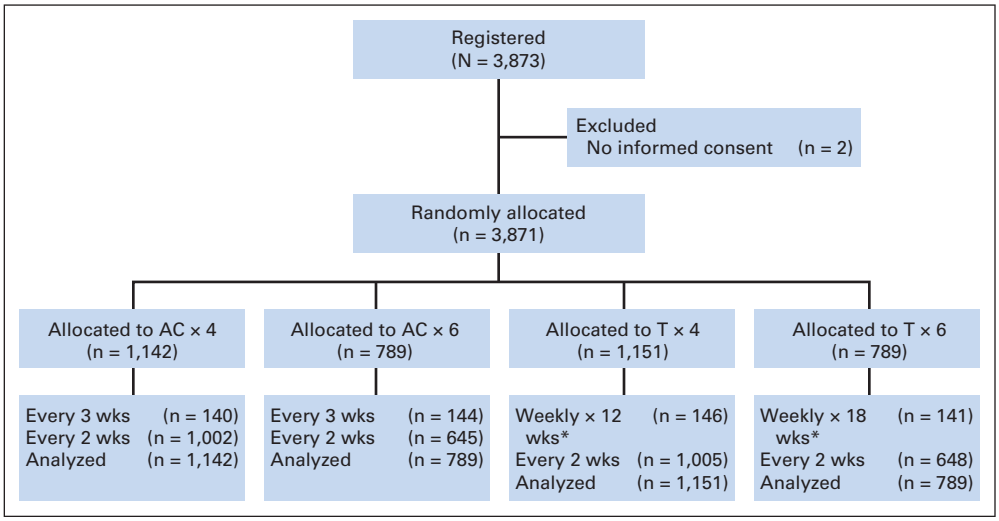

Fig 1. CONSORT diagram. Randomized controlled trial: patients registered, treatment-arm assignments, and exclusions. Cyclophosphamide and doxorubicin (AC) was administered as noted as doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 given every 2 or 3 weeks for four or six cycles. T (paclitaxel) was administered as 80 mg/m^2 when given weekly for 12 or 18 weeks (3 weeks equaling one cycle) or as 175 mg/m^2 when administered every 2 weeks for four to six cycles.

RFS and OS distributions were estimated using the Kaplan-Meier product limit technique.[14] Log-rank tests compared distributions of two or more groups.[15] 95% CIs of time-to-event variables used the method of Hosmer and Lemeshow.[16]

Predictive probability was calculated using Bayesian methods that assumed an exponential time-to-event distribution with independent and non-informative prior distributions about the parameters.[17] Efficacy analyses used an intention-to-treat approach. Adverse events were reported using National Cancer Institute Common Toxicity Criteria version 4.0.[18] Additional statistical information is available in the Appendix (online-only).

RESULTS

A total of 3,871 patients were enrolled onto the study between 2002 and 2010 (Fig 1). Patient characteristics and baseline clinicopathologic variables are listed in Table 1; these were well balanced between the AC and T arms. Of note is that 90% of patients had node-negative disease and 68% of patients had hormone-receptor–positive disease. Only 48% of patients had their tumors assayed for HER2, and, among those assayed, 84% were negative.

Table 1. Patient Characteristics by Regimen

Characteristic	Percent of Patients by Regimen		
	AC (n = 1,931)	T (n = 1,940)	All Regimens (n = 3,871)
Age ≥ 50 years	61	62	61
Non-white race	16	17	16
Premenopausal	40	39	40
Node-negative	89	90	90
Tumor size ≤ 2 cm	66	63	65
HR-positive tumors	68	68	68
HER2-negative tumors*	85	84	84
High grade	46	45	46
Mastectomy	35	35	35

Abbreviations: AC, doxorubicin/cyclophosphamide; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; T, paclitaxel.
*Tumoral HER-2 was measured in 48% of patients. Table entries are based upon patients with HER-2 data.

At a median follow-up period of 6.1 years, there were 437 RFS events; 192 events were in the AC arms and 245 were in the T arms. The HR from the stratified proportional hazards model was 1.26 (UCB, 1.48) favoring AC. Because the upper limit of the confidence interval exceeds an HR of 1.3, the upper boundary that would be required to conclude noninferiority, we cannot conclude noninferiority of T compared with AC. A total of 266 patients died; 116 patients in the AC arms, and 150 patients in the T arms. The HR from a corresponding stratified model was 1.27 (UCB, 1.56), also favoring AC, and therefore noninferiority of T compared with AC could not be shown since the upper limit of the CI was above 1.3. Based on the current data, with 437 RFS events, the Bayesian predictive probability of concluding noninferiority of T compared with AC if the trial had achieved 567 RFS events is less than 5%. Ad hoc analyses to examine the impact on clinical outcome of changing treatment scheduling (from every 3 weeks to every 2 weeks) and nodal involvement (from zero to zero to three) gave results in keeping with those of the primary analyses that included the entire study group (data not shown).

Results of multivariable proportional hazards modeling also indicated that T was not shown to be noninferior to AC for either RFS or OS, after adjusting for the effects of tumor size, number of positive nodes, hormone receptor status, or menopausal status (Appendix Table A1).

RFS and OS distributions are illustrated in Figure 2. The 5-year RFS was 91% for patients treated with AC and 88% for those treated with T. OS at 5 years was 95% for patients treated with AC and 94% for those treated with T. Also shown in Figure 2 is RFS by arm within hormone receptor status (positive or negative). T had a numerically poorer outcome than AC regardless of hormone receptor status. Figure 3 shows RFS for all four arms and indicates a lack of interaction between regimen and duration. These findings are consistent across duration and regimen questions; that is, six cycles of therapy is not superior to four cycles for patients treated with AC or T and T is not equivalent to AC regardless of treatment duration.

A total of 3,754 patients were evaluable for toxicity that occurred during treatment. As expected, the incidence of any grade 3 or higher hematologic toxicity was considerably higher in the AC arms compared with the T arms (four cycles, 29%; six cycles, 38%).

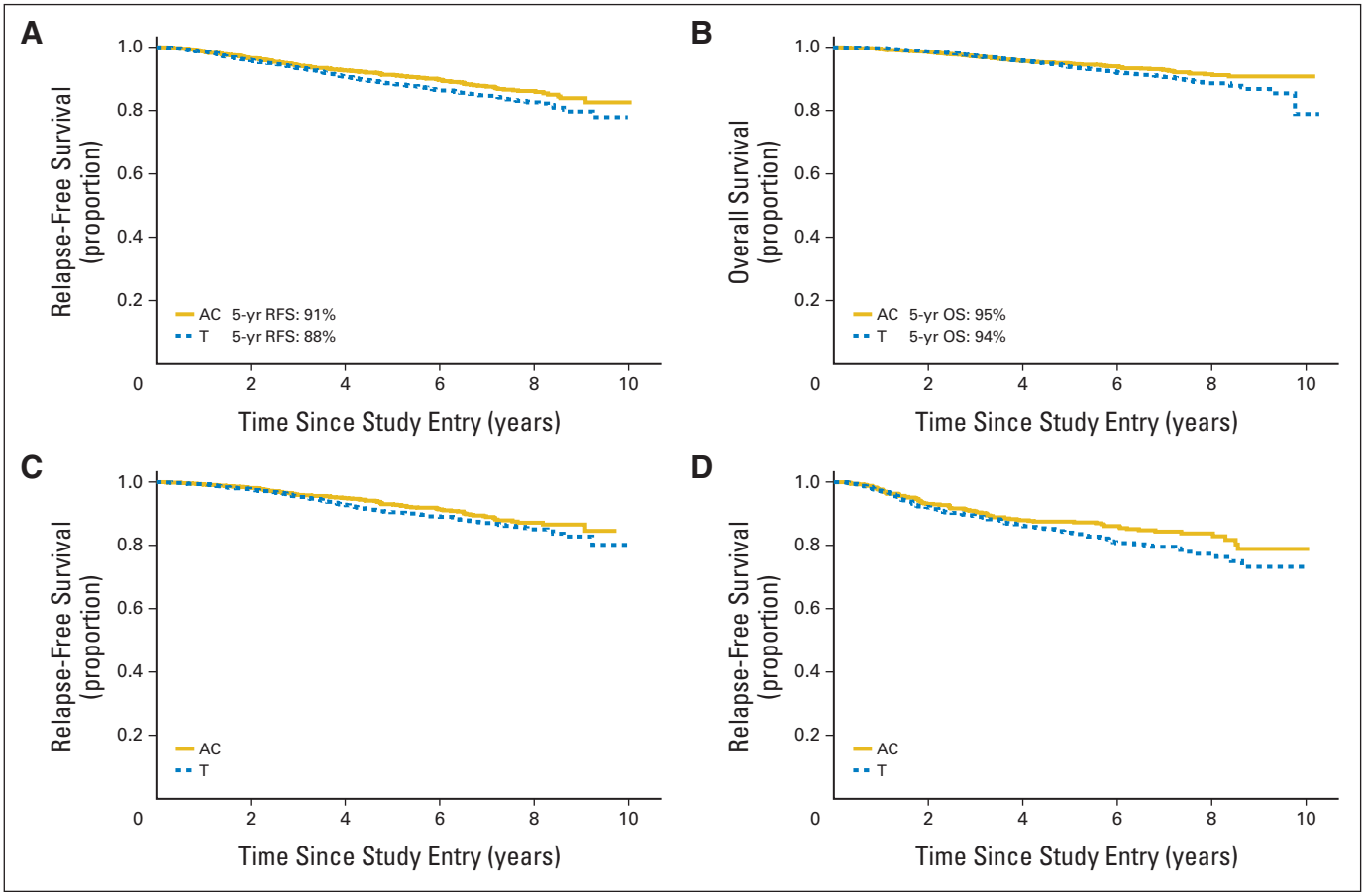

Fig 2. (A) relapse-free survival (RFS) for all patients (hazard ratio [HR] 1.26; 95% CI, 1.05 to 1.53) favoring doxorubicin and cyclophosphamide (AC); (B) overall survival (OS) for all patients (HR 1.27; 95% CI, 1.00 to 1.62) favoring AC; (C) RFS for hormone receptor–positive tumors; (D) RFS for hormone receptor–negative tumors. T, paclitaxel; yr, year.

Also as expected, neuropathy was the most frequent nonhematologic adverse event and was more common in the T than the AC arms (grade 3 events in the six-cycle T arm, 12%; grade 3 events in the four-cycle T arm, 5%). Grade 4 neurotoxicity was rare, occurring in less than 1% of patients. Incidence of other nonhematologic toxicities was not more than 3%. Selected grade 3 and 4 toxicities are listed in Table 2. Cardiac toxicity was infrequent in all of the treatment arms (Appendix Table A2). Two cardiac deaths (both on AC arms) were attributed to protocol treatment. One patient, who was randomly assigned to the AC × 4 arm under the every-3-week schedule, died of a myocardial infarction 96 days after enrollment. The other patient, who was randomly assigned to the AC × 6 arm, died shortly after completing protocol therapy, 127 days after enrollment, as a result of left-ventricular dysfunction.

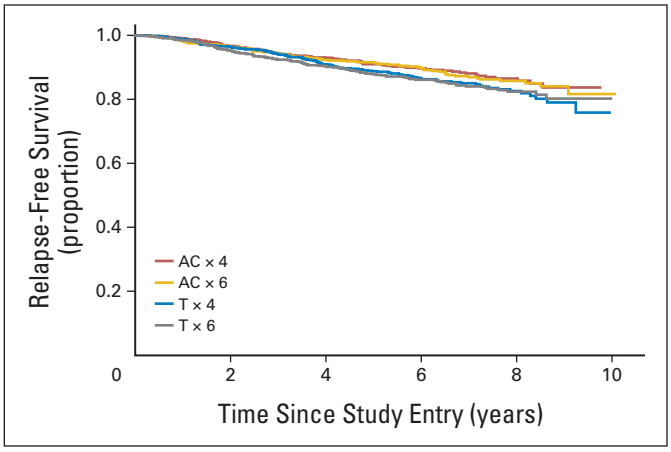

Fig 3. Relapse-free survival by treatment arm. Doxorubicin and cyclophosphamide (AC) was administered as noted as doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 given every 2 or 3 weeks for four or six cycles. Paclitaxel (T) was administered as 80 mg/m^2 when given weekly for 12 or 18 weeks (3 weeks equaling one cycle) or as 175 mg/m^2 when administered every 2 weeks for four or six cycles.

Seven patients, all on the AC arms, developed acute myelogenous leukemia or myelodysplastic syndrome between 11 and 34 months after enrollment onto the study. All seven patients died, and their deaths are considered to be related to treatment.

Causes of death are listed in Table 3. In total, 266 patients died; 116 patients who were receiving AC and 150 who were receiving T. Of these, 147 patients' deaths were known to be related to breast cancer (AC, 60 deaths; T, 87 deaths). The cause of death for the remaining 110 patients was not related to breast cancer or treatment, was unconfirmed breast cancer, or was unknown.

DISCUSSION

CALGB 40101 was designed to test the potential noninferiority of T compared with AC, with the hypothesis that if T was noninferior it

Table 2. Selected Grade 3 and 4 Adverse Events During Protocol Therapy by Treatment Arm

Adverse Event	% of Events by Treatment Arm							
	AC × 4 (n = 1,107)		AC × 6 (n = 766)		T × 4 (n = 1,119)		T × 6 (n = 762)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hemoglobin	4	≤ 1	6	1	< 1	0	1	≤ 1
Neutropenia	8	18	10	23	2	1	2	1
Febrile neutropenia	5	< 1	6	< 1	< 1	0	0	0
Thrombocytopenia	1	< 1	3	1	< 1	0	0	0
Neuropathy (sensory and/or motor)	< 1	0	< 1	0	5	< 1	12	< 1
Diarrhea	1	< 1	2	0	1	0	1	0
Vomiting	3	0	3	0	< 1	< 1	0	0
Fatigue	3	< 1	6	< 1	1	< 1	3	0
Arthralgia	< 1	0	< 1	0	2	0	2	< 1

NOTE. Doxorubicin and cyclophosphamide (AC) was administered every 2 or 3 weeks as noted as doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 for four or six cycles. T (paclitaxel) was administered as 80 mg/m^2 when given weekly for 12 or 18 weeks (3 weeks equaling one cycle) or as 175 mg/m^2 when administered every 2 weeks for four or six cycles.

would provide women with good-prognosis primary breast cancer a less toxic, equally efficacious option. Because we were not able to demonstrate noninferiority for either RFS or OS, single-agent T cannot be recommended as a standard regimen for women with primary breast cancer and zero to three positive axillary nodes. In addition, there was no subgroup in which clinical outcome from T was noninferior to that of AC. There was also no differential effect of agent by duration of therapy (four *v* six cycles).

The majority of patients of our study received dose-dense AC and dose-dense T. The decision to convert to this schedule was based on the publication of CALGB 9741, which demonstrated that dose-dense AC followed by T was superior to AC followed by T, given every 3 weeks.[11] Despite the unexpected protocol modifications to schedule and eligibility after accrual had begun, exploratory ad hoc comparisons by cycle length of every 3 weeks versus every 2 weeks and by nodal involvement of node-negative versus either node-negative or node-positive disease gave results in keeping with those of the overall analyses. Thus, our conclusions are the same regardless of modifications to treatment schedule and nodal status.

Multiagent chemotherapy became a standard of antineoplastic therapy since regimens such as mustargen, vincristine, procarbazine, and prednisone (MOPP) for Hodgkin's lymphoma and complex regimens for acute lymphoblastic leukemia were shown to be curative. Based on these findings and principles, adjuvant regimens for the treatment of localized breast cancer have exclusively been multiagent in nature. However, in the setting of metastatic breast cancer, single-agent chemotherapy has in some studies been associated with equal survival rates when compared with intensive multiagent regimens. Our study would suggest that single-agent taxane as adjuvant therapy is not optimal therapy for these women.

Table 3. Causes of Death by Treatment Regimen

Cause of Death	No. of Patients Who Died Within Regimen		
	AC (n = 1,931)	T (n = 1,940)	Total (n = 3,871)
Breast cancer	60	87	147
Treatment-related death	9	0	9
AML/MDS	7	0	7
Cardiotoxicity	2	0	2
Other	47	63	110
Total No. of deaths	116	150	266

Abbreviations: AC, doxorubicin/cyclophosphamide; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; T, paclitaxel.

The precise role of taxanes in adjuvant breast cancer regimens remains unclear. Though regimens such as AC followed by a taxane have often been used in women with high-risk primary breast cancer, AC alone has remained a standard regimen for many better-risk patients with primary breast cancer. Eastern Cooperative Oncology Group trial 2197 compared four cycles of AC as the standard of care, with four cycles of doxorubicin and docetaxel in women with zero to three positive nodes, and found that there was no survival advantage to the combination of doxorubicin and docetaxel over AC, and that there was no survival advantage to the combination of doxorubicin and docetaxel (AT) over AC, and that AT was more toxic.[5] Of note is that 66% of these patients had node-negative disease, compared with 90% in our study. Docetaxel and cyclophosphamide has been widely adopted in practice based on a modest size, single trial that demonstrated superiority for this regimen over AC in women with node-negative and node-positive disease.[6] Docetaxel and cyclophosphamide is also associated with substantial toxicity and our hope had been that single-agent taxane therapy might be noninferior and less toxic. Given the results of our trial, AC (which had a 5-year RFS of 91% and a 5-year OS of 95%) but not single-agent T remains among the reasonable options for patients with lower-risk disease based on tumor volume and tumor characteristics. The use of adjuvant chemotherapy is evolving and chemotherapy use is increasingly based on molecular features of the tumor (such as multigene prediction assays) to determine which patients should receive chemotherapy. Molecular characteristics of the tumor may similarly become helpful in selecting specific chemotherapy regimens.

In summary, we could not conclude noninferiority of single-agent T compared with AC to treat women with zero to three positive axillary nodes in regard to either relapse-free or overall survival. AC was more toxic, and all treatment-related deaths occurred in patients

treated with AC. These findings support AC as an option as standard of care, whereas our previous findings support four cycles of therapy as a standard duration of therapy for these patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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GLOSSARY TERMS

estrogen receptor (ER): ligand-activated nuclear proteins, belonging to the class of nuclear receptors, present in many breast cancer cells that are important in the progression of hormone-dependent cancers. After binding, the receptor-ligand complex activates gene transcription. There are two types of estrogen receptors (ERα and ERβ). ERα is one of the most important proteins controlling breast cancer function. ERβ is present in much lower levels in breast cancer, and its function is uncertain. Estrogen receptor status guides therapeutic decisions in breast cancer.

HER2/*neu* (human epidermal growth factor receptor 2): also called ErbB2. HER2/*neu* belongs to the epidermal growth factor receptor (EGFR) family and is overexpressed in several solid tumors. Like EGFR, it is a tyrosine kinase receptor whose activation leads to proliferative signals within the cells. On activation, the human epidermal growth factor family of receptors are known to form homodimers and heterodimers, each with a distinct signaling activity. Because HER2 is the preferred dimerization partner when heterodimers are formed, it is important for signaling through ligands specific for any members of the family. It is typically overexpressed in several epithelial tumors.

overall survival: the duration between random assignment and death.

progesterone receptor (PgR): nuclear proteins that are activated by the hormone progesterone in breast cancer cells that are hormone-dependent.

Appendix

Per National Cancer Institute policy, our study was monitored every 6 months by an independent data and safety monitoring board (DSMB), beginning in November 2002. Preplanned interim analyses of noninferiority used the stratified univariable proportional hazards model described above. The Lans-Demets spending function was used in interim analyses and assumed an overall one-side significance level of 0.05 (DeMets et al: Stat Med 13:1341-1352, 1994). The first formal interim analysis, scheduled at 10% of the total expected events, was conducted in June 2006. Thereafter, interim analyses were conducted once every two years until June 2008. In June 2010, the DSMB released the results for the four- versus six-cycle comparison. In December 2012, the DSMB released the results of the doxorubicin and cyclophosphamide versus paclitaxel noninferiority comparison.

Study data were collected by Cancer and Leukemia Group B (CALGB; Alliance) Statistics and Data Center and were stored in the CALGB (Alliance) database. Data quality was ensured by review of data by the Statistics and Data Center and by the study chairperson per group policies. All analyses were conducted by CALGB (Alliance) statisticians. The data cutoff for this report was December 2012.

Table A1. Multivariable Proportional Hazards Models: Observed Effects on RFS and OS (n = 3,862)

Variable	Comparison of Worse:Better for HR	RFS (11% of events)			OS (7% of events)		
		HR	95% CI*	*P*	HR	95% CI*	*P*
Agent	T:AC	1.25	1.47 (UCB)	N/A†	1.25 (UCB)	1.53	N/A†
Tumor size, cm	2:1.5	1.15	1.10 to 1.21	< .0001	1.19	1.12 to 1.27	< .0001
No. of positive nodes	2:0	1.21	0.81 to 1.81	.35	1.54	0.94 to 2.51	.089
Hormone receptor	Neg:pos	1.74	1.44 to 2.11	< .0001	2.22	1.74 to 2.83	< .0001
Menopausal status	Post:pre	1.15	0.95 to 1.39	.17	1.73	1.33 to 2.26	< .0001

Abbreviations: AC, doxorubicin/cyclophosphamide; HR, hazard ratio; N/A, not applicable; Neg, negative; OS, overall survival; pos, positive; post, postmenopausal; pre, premenopausal; RFS, relapse-free survival; T, paclitaxel; UCB, upper confidence bound.
*One-sided 95% CI.
†*P* value is not applicable. Noninferiority is tested by UCB (> 1.3 for both RFS and OS models).

Table A2. Grade ≥ 3 Cardiotoxicity During Protocol Therapy

Adverse Event	No. of Events by Treatment Arm											
	AC × 4 (n = 1,107)			AC × 6 (n = 766)			T × 4 (n = 1,119)			T × 6 (n = 762)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
LV systolic dysfunction	2	0	0	3	2	1	0	0	0	1	1	0
Restrictive cardiomyopathy	0	0	0	1	0	0	0	0	0	0	0	0
General cardiac	0	0	1	0	0	0	1	0	0	1	0	0

NOTE. Doxorubicin and cyclophosphamide (AC) was administered every 2 or 3 weeks as noted as doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 for four or six cycles. T (paclitaxel) was administered as 80 mg/m^2 when given weekly for 12 or 18 weeks (3 weeks equaling one cycle) or as 175 mg/m^2 when administered every 2 weeks for four or six cycles.
Abbreviation: LV, left ventricular.