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ORIGINAL REPORT

Phase III Trial Comparing Doxorubicin Plus Cyclophosphamide With Docetaxel Plus Cyclophosphamide As Adjuvant Therapy for Operable Breast Cancer

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ABSTRACT

Purpose
The combination of doxorubicin and cyclophosphamide (AC) is a standard adjuvant chemotherapy regimen. Studies of docetaxel and cyclophosphamide (TC) in metastatic breast cancer (MBC) showed promise in MBC. In 1997, we initiated a randomized adjuvant trial of TC compared with standard-dose AC with a primary end point of disease-free survival (DFS).

Patients and Methods
Patients were eligible if they had stage I to III operable invasive breast cancer with complete surgical excision of the primary tumor. Between June 1997 and December 1999, 1,016 patients were randomly assigned to four cycles of either standard-dose AC (60 and 600 mg/m^2, respectively; n = 510) or TC (75 and 600 mg/m^2, respectively; n = 506), administered intravenously every 3 weeks as adjuvant chemotherapy. Radiation therapy (as indicated) and tamoxifen, for patients with hormone receptor–positive disease, were administered after completion of chemotherapy.

Results
Both treatment groups (TC and AC) were well balanced with respect to major prognostic factors. Patients were observed through 2005 for a median of 5.5 years. At 5 years, DFS rate was significantly superior for TC compared with AC (86% *v* 80%, respectively; hazard ratio [HR] = 0.67; 95% CI, 0.50 to 0.94; P = .015). Overall survival rates for TC and AC were 90% and 87%, respectively (HR = 0.76; 95% CI, 0.52 to 1.1; P = .13). More myalgia, arthralgia, edema, and febrile neutropenia occurred on the TC arm; more nausea and vomiting occurred on the AC arm as well as one incident of congestive heart failure.

Conclusion
At 5 years, TC was associated with a superior DFS and a different toxicity profile compared with AC.

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INTRODUCTION

Four cycles of doxorubicin and cyclophosphamide (AC) chemotherapy has become a standard adjuvant regimen. AC was demonstrated to be equivalent to 6 months of classic cyclophosphamide, methotrexate, and fluorouracil in two separate National Surgical Adjuvant Breast and Bowel Project (NSABP) studies (NSABP-15 and NSABP-23).[1,2] No chemotherapy regimen administered for four cycles has proven to be superior to AC.

The taxanes were introduced into clinical practice in the early 1990s, first for metastatic breast cancer (MBC) and then in the adjuvant setting.[3-5] In a head-to-head comparison of docetaxel to paclitaxel in MBC, Jones et al[6] showed that docetaxel was superior to paclitaxel on a schedule of every 3 weeks. We became interested in evaluating docetaxel in the adjuvant setting in the mid-1990s, but there was inadequate safety data to study docetaxel combined with doxorubicin. About the same time, Valero[7] evaluated the combination of docetaxel and cyclophosphamide (TC), which was active in MBC and devoid of cardiotoxicity. Accordingly, we decided to test TC against standard AC in a randomized prospective trial of these two adjuvant chemotherapy regimens. Toxicity data and a planned interim analysis have been reported previously in abstract

form.[8,9] In this report, we describe the final planned analysis of this trial, now with 5.5 years of follow-up.

PATIENTS AND METHODS

Study Design

This was a phase III randomized prospective clinical trial comparing four cycles of AC with four cycles of TC as adjuvant chemotherapy for women with operable stage I to III invasive breast cancer. Patients were randomly assigned to four cycles of either standard-dose AC (60 and 600 mg/m^2, respectively) or TC (75 and 600 mg/m^2, respectively) administered by intravenous infusion over 30 to 60 minutes on day 1 of each 21-day cycle for four cycles as adjuvant treatment after complete surgical excision of the primary tumor (Fig 1). Chemotherapy was administered before radiation therapy (XRT) when XRT was indicated (breast conservation or postoperative XRT for patient with four or more involved axillary lymph nodes). On completion of four cycles of chemotherapy (± XRT), tamoxifen was administered to all patients with hormone receptor–positive breast cancer for 5 years.

The protocol was approved by a central institutional review board with jurisdiction over the sites that registered patients onto the study, and all patients were required to sign an informed consent form before being enrolled onto the study.

Patients

Eligible patients were between the ages of 18 and 75 years with a Karnofsky performance status of ≥ 80% and no evidence of metastatic disease by standard laboratory and radiologic testing. Before treatment, a complete surgical excision of the primary tumor (lumpectomy and axillary dissection or modified radical mastectomy) was performed. No neoadjuvant chemotherapy was permitted. Eligible primary tumor size was ≥ 1.0 cm and less than 7.0 cm. Patients were required to have an absolute neutrophil count of ≥ 1,400/μL, platelet count of ≥ 100,000/μL, hemoglobin of ≥ 9 g/dL, direct bilirubin of ≤ 1.5 mg/dL, serum creatinine less than 1.5 mg/dL, and AST ≤ 2.5× the upper limit of normal. Patients had no active serious infection or underlying medical condition and had not received any prior chemotherapy or hormonal therapy. Pregnant and lactating females were excluded.

Treatment

Treatment consisted of four 3-week cycles of therapy. If disease progression or unacceptable toxicity occurred, the patient was taken off treatment. Patients were premedicated for docetaxel with oral dexamethasone 8 mg twice daily starting 1 day before each infusion of docetaxel and continuing for a total of five doses. AC (60 and 600 mg/m^2, respectively) or TC (75 and 600 mg/m^2, respectively) was administered by intravenous infusion over 30 to 60 minutes on day 1 of each 21-day cycle. Actual body-surface area was used without any limit on total doses of drug. Postoperative XRT and tamoxifen were administered after the completion of all chemotherapy, for appropriate patients. At the time this trial was initiated, there was no general use of aromatase inhibitors. Therefore, tamoxifen was the mainstay of hormonal therapy in this study.

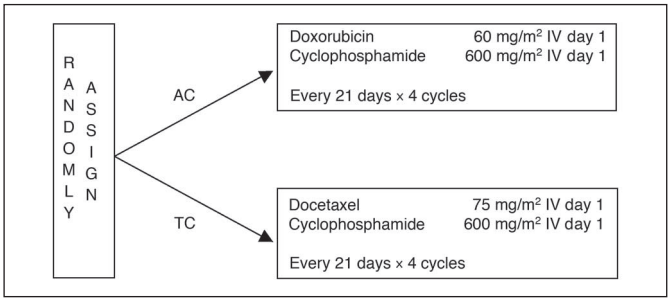


Fig 1. Treatment schema. AC, doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide; IV, intravenous.

Assessments

Validation of inclusion and exclusion criteria, completion of the informed consent, a pregnancy test (when indicated), and a medical history were completed at baseline. A physical examination including vital signs, height and weight, assessment of the Eastern Cooperative Oncology Group (ECOG) performance status, CBC with differential and platelet count, disease assessment, and laboratory tests (total bilirubin, serum creatinine, AST, ALT, alkaline phosphatase, and serum calcium) were conducted at baseline. Toxicity was assessed at each patient visit and for 30 days after the last dose. Assessment of disease status (eg, computed tomography, ultrasound, routine x-rays, bone scans, and so on) and left ventricular ejection fraction was performed by echocardiogram or multinucleated gated angiography when clinically indicated during the study. No formal comparison of cardiac function between treatment arms was planned for this study. Follow-up was done at 6-month intervals for 5 years and annually thereafter to 7 years. Lab work, annual chest x-rays, mammograms (if indicated), and assessments of health status occurred at these visits.

Criteria for Assessing Toxicity

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 1). Study-specific unacceptable toxicities were defined as more than grade 3 nonhematologic toxicity (excluding nausea and vomiting), grade 4 vomiting despite antiemetics, and grade 4 hematologic toxicity according to the National Cancer Institute Common Toxicity Criteria despite two treatment delays. Grade 4 neutropenia was ≥ 7 days in duration or was accompanied by fever (single elevation in oral temperature to > 38.5°C, or three elevations to > 38°C during a 24-hour period) requiring parenteral antibiotics. For this study, fluid retention was defined as the development of edema or cytologically negative pleural effusion, ascites, or pericardial effusion; all graded as mild, moderate, or severe. The definition of edema for this study was edema more than trace. Patients were taken off treatment if administration of any study drug was delayed more than 2 weeks as a result of drug-related toxicities. No dose reductions in AC or TC were permitted. No prophylactic growth factors were used and the use of oral prophylactic antibiotics was at the discretion of the treating physician.

Statistical Analysis

Registration, random assignment, and stratification (by age and nodal status) as well as data analyses were performed in the Biostatistics and Medical Writing Section of US Oncology Research, Houston, TX.

To have 90% power to detect a 10% improvement in 5-year disease-free survival (DFS) in favor of TC, from 0.7 to 0.8, with a two-sided type I error rate of 0.05, 1,016 patients were needed to be randomly assigned at a rate of 442 patients per year and observed for 5 years. Interim analysis was carried out with $\alpha = .0076$. The final analysis was done with $\alpha = .0434$ for a sum of $\alpha = .05$. The planned interim analysis was previously reported.[9] A Cox test was used to test the hazard ratio (HR) equal to 1 to coincide with the sample size of 174 events.

DFS was measured from the date of first dose until the date of any relapse of breast cancer (local or distant), a new breast cancer or other type of cancer, death as a result of any cause without relapse of breast cancer, or last patient contact. Survival was measured from the date of first dose to the date of death (any cause) or to the date of last contact. DFS and overall survival (OS) were assessed using the Kaplan-Meier method,[10] and log-rank tests were used to compare the differences between the resulting curves. χ^2 statistics were used to test the differences in toxicities between the two treatment arms. Treatment-related toxicities were reported using Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) and summarized by highest grade per patient. Patient demographics and tumor characteristics were also compared between treatment arms. The analysis was conducted on the intent-to-treat population, which included all randomly assigned patients, and the safety analysis included all patients who received at least one dose of study drug. For ease of comparison, the percentage of patients alive or disease free at 3 and 5 years were summarized graphically (as in Figs 2 and 4). All statistical analyses were performed using SAS version 8 (SAS Institute, Cary, NC) and Statistica software (version 6; StatSoft, Tulsa, OK).

Table 1. Patient Characteristics at Baseline

Characteristic	TC (n = 506) No. of Patients	TC (n = 506) %	AC (n = 510) No. of Patients	AC (n = 510) %	Total (N = 1,016) No. of Patients	Total (N = 1,016) %
Age, years						
Median	52		51		51	
Range	27-77		27-77		27-77	
Race/Ethnicity						
White	432	85.5	430	84	862	85
Black	33	6.5	41	8	74	7
Hispanic	36	7	33	7	69	7
Other	5	1	6	1	11	1
Stage at registration						
I	104	20	112	22	216	21
II	373	74	364	71	737	72
III	27	5	34	7	61	6
Unknown	2	1	0	0	2	1
Histology						
Infiltrating ductal	446	88	439	86	885	87
Infiltrating lobular	34	7	38	7.5	72	7
Mixed	26	5	33	6.5	59	6
Hormone receptor status						
ER positive, PR positive	298	59	288	56	586	58
ER negative, PR positive	17	3	19	4	36	3.5
ER positive, PR negative	52	10	45	9	97	9.5
ER negative, PR negative	137	27	157	31	294	29
Unknown	2	1	1	< 1	3	< 1
Positive nodes						
0	239	47	248	49	487	48
1-3	209	41	212	42	421	41
≥ 4	58	12	50	9	108	11

Abbreviations: AC, doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide; ER, estrogen receptor; PR, progesterone receptor.

RESULTS

Patient Characteristics

Between July 1, 1997, and January 5, 2000, a total of 1,016 patients with operable stage I to III invasive breast cancer were enrolled onto this study comparing AC versus TC as adjuvant treatment. At random assignment, patients were stratified by age (< 50 or ≥ 50 years) and by nodal status (none, one to three, or ≥ four nodes). Patient characteristics were well balanced between treatment arms; 42% of patients in both arms were less than 50 years of age. The demographics of all patients are listed in Table 1. The majority (71%) of patients had breast cancer that was estrogen receptor (ER) positive and/or progesterone receptor (PR) positive; 27% of the TC patients and 31% of the AC patients were ER negative/PR negative. Hormone receptor status is also listed in Table 1. There were two patients in the TC arm and one patient in the AC arm with unknown hormone receptor status. However, their inclusion did not affect the overall response, and these three patients were counted in the total population. The number of patients with node-negative disease was balanced between groups (47% TC and 49% AC); 12% of TC and 9% of AC patients had ≥ four positive nodes.

Ninety-three percent of patients in the TC arm completed their treatment (469 patients completed all four cycles), and 95% of patients in the AC arm completed their treatment (484 patients completed all four cycles). The median dose administered to patients in the TC arm was 135 mg of docetaxel (range, 75 to 210 mg) and 1,077 mg of cyclophosphamide (range, 110 to 1,680 mg), whereas patients in the AC arm received 108 mg of doxorubicin (range, 60 to 148 mg) and 1,086 mg of cyclophosphamide (range, 100 to 1,998 mg). Dose-intensity was 99.8% in the TC arm and 99.4% in the AC arm.

Table 2. Events and Reasons for Study Discontinuation

Event	TC (n = 506) No. of Patients	TC (n = 506) %	AC (n = 510) No. of Patients	AC (n = 510) %
Relapse or second cancer	71	14	103	20
Death, any cause	55	11	73	14
Death without relapse	8	2	15	3
Death on treatment*	2	< 1	0	0
Sites of relapse†				
Local	8	2	15	3
Distant	43	8.5	52	10
Local/distant	8	2	13	3
Total patients surviving	451	89	437	86

NOTE. Median follow-up time was 66 months.
Abbreviations: AC, doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide.
*Two deaths (one unrelated cardiac death and one related death from neutropenia and sepsis).
†Patients may have had more than one site of relapse.

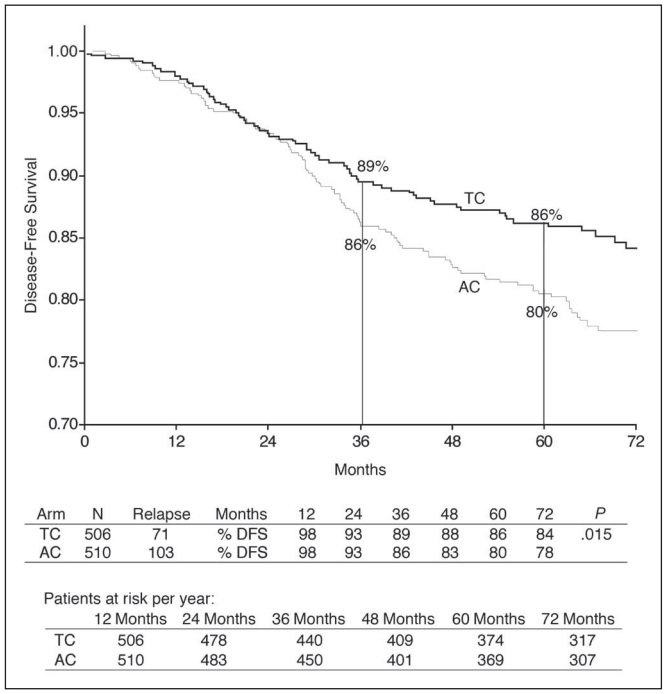


Fig 2. Disease-free survival (DFS). AC, doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide.

Outcome

Data on events used to calculate DFS and sites of relapse are listed in Table 2. The median follow-up at 174 events (April 29, 2005), which prompted this planned analysis, was 66 months. The primary end point of this trial was the overall DFS (Fig 2). For comparison at 5 years, the DFS rate for patients receiving TC was 86% compared with 80% for patients receiving AC (HR = 0.67; 95% CI, 0.50 to 0.94; $P = .015$). An exploratory analysis of DFS according to major subgroups (age, receptor status, and nodal status) is shown in Figure 3. Age and nodal status were pretreatment stratification factors. The number of patients is small in most of these subgroups, but evidence favoring TC over AC is apparent in all subgroups in this exploratory analysis. The study was not powered to detect differences in subgroups. The majority of patients had hormone receptor–positive disease and received adjuvant tamoxifen. We had no plan in place to capture information about the use of aromatase inhibitors during the follow-up period.

OS, a secondary end point in this trial, is shown in Figure 4. For comparison at 5 years, the OS rate for women treated with TC was 90% compared with 87% for women treated with AC (HR = 0.76; 95% CI, 0.52 to 1.1; $P = .13$), thus TC tended to improve OS compared with AC.

Toxicity

Overall, toxicities were fairly similar between groups with some exceptions. TC patients experienced significantly more grade 1 and 2 edema, myalgia, and arthralgia ($P < .01$), whereas AC patients had more grade 1 to 4 nausea and vomiting ($P < .01$). In the AC group, one patient died from congestive heart failure, and four patients died from myocardial infarction. In the TC group, no case of congestive heart failure was observed; however, two patients died from myocardial infarction. There was more fever and neutropenia observed with TC (25 patients, 5%) compared with AC (13 patients, 2.5%; $P = .07$). Two patients died while receiving TC (one unrelated cardiac death and one death with sepsis and neutropenia); no patients died during treatment with AC. Clinically significant toxicities are listed in Table 3. No cases of leukemia or myelodysplasia were observed.

DISCUSSION

The purpose of this trial was to compare the DFS in patients treated with four cycles of standard AC or four cycles of the nonanthracycline regimen TC. To that end, we demonstrated a significant improvement in DFS for TC compared with AC (5-year DFS rate, 86% for TC *v* 80% for AC; HR = 0.67; $P = .015$). A trend in improved OS rate was also apparent (90% for TC *v* 87% for AC; HR = 0.76; $P = .13$). With longer follow-up, this difference in OS may become statistically significant because 71% of the patients in this trial had hormone receptor–positive breast cancer. The other observation was the difference in toxicity profile between TC and AC. AC was associated with significantly more nausea and vomiting (all grades as well as grades 3 and 4), but TC had more low-grade edema, myalgia, and arthralgia secondary to the use of docetaxel. TC was also associated with a somewhat higher rate of fever and neutropenia compared with AC (5% *v* 2.5%,

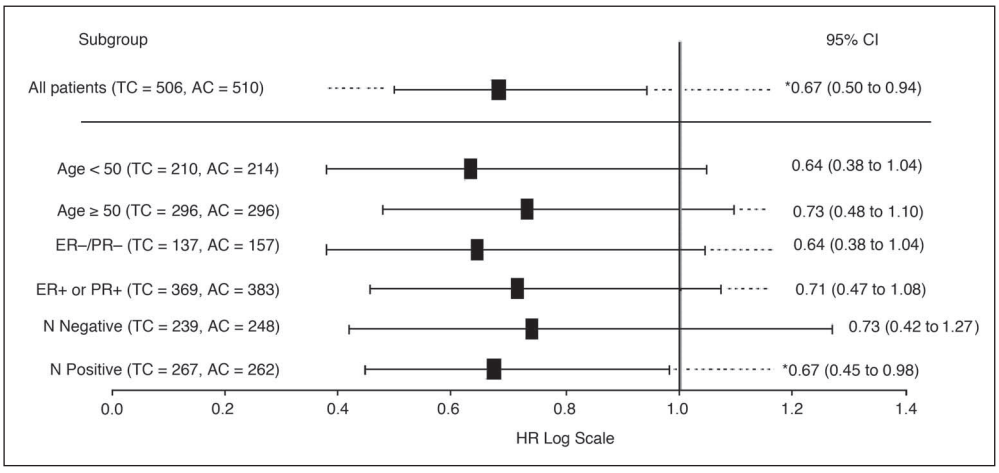
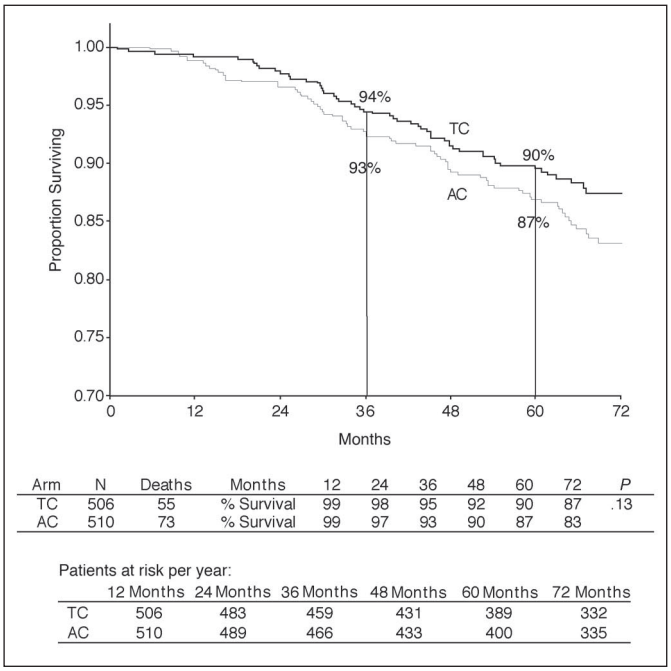


Fig 3. Forest plot of disease-free survival (DFS) hazard ratios (HR) of major subgroups (exploratory analysis). (*), $P < .05$. AC, doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide; ER, estrogen receptor; PR, progesterone receptor; N, node.



Arm	N	Deaths	Months	12	24	36	48	60	72	*P*
TC	506	55	% Survival	99	98	95	92	90	87	.13
AC	510	73	% Survival	99	97	93	90	87	83	

Patients at risk per year:

	12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
TC	506	483	459	431	389	332
AC	510	489	466	433	400	335

Fig 4. Overall survival. AC, doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide.

respectively; $P = .07$), but both of these rates are within the ranges for AC-type regimens.[11] More peripheral phlebitis was observed in the TC arm for patients without venous access devices. Neither prophylactic antibiotics nor leukocyte growth factors were routinely used in this trial. Interestingly, a single incident of congestive heart failure was observed in the AC arm (none in the TC arm). AC is known to be cardiotoxic, with a usual rate of less than 1% in patients treated with four cycles of AC.[12,13] TC is not known to be cardiotoxic[7]; however, no formal comparison of cardiac function between treatment arms was incorporated into the trial's design.

Recently, a large adjuvant study has been reported by Goldstein et al.[11] In this ECOG trial (E2197), 2,952 patients were randomly assigned to four cycles of AC or four cycles of doxorubicin and docetaxel (AT). At 4 years, the DFS rate was identical (87%) in both groups of patients, as was OS. More toxicity was observed with AT (rates of fever and neutropenia were 19% for AT *v* 6% for AC), and more deaths on treatment were observed with AT.

We can only speculate why the AT results were not different from AC, whereas TC was superior in our trial. We studied a slightly higher risk group of patients (more node-positive disease). A higher dose of docetaxel was used (75 mg/m^2 in our trial *v* 60 mg/m^2 in the ECOG trial), and there is a proven dose-response relationship of docetaxel in MBC.[14]

In our trial, we had no cap on the actual doses of chemotherapy and used actual body-surface area for calculations of drug doses. Finally, there may be more synergism between docetaxel and cyclophosphamide than previously suggested.[7] Regardless of the possible explanations, TC proved to be superior to AC in our trial, achieving the primary end point of improved DFS for the entire group of women under study.

In a subset of breast cancer that was previously considered to be anthracycline dependent, Slamon et al[15] have shown that the combination of docetaxel, carboplatin, and trastuzumab is as effective as standard AC followed by docetaxel with trastuzumab. Furthermore, they have shown that only patients with a mutation in topoisomerase II isomerase, which occurs in only 35% of human epidermal growth factor receptor 2 (*HER2*) – dependent breast cancers, have the cancers that seem to require anthracyclines. Our study further confirms that anthracyclines are not required for superior antitumor efficacy. Although analysis of our data for *HER2* status and topoisomerase II status would be interesting, this has not been done and may be the subject of a future report, if tissue can be obtained.

We conclude that our study has established a new standard nonanthracycline regimen, TC, for the adjuvant treatment of early-stage breast cancer. It has no apparent cardiotoxicity, and

Table 3. Frequency of the Most Common Adverse Events (all grades)

	TC Patients (n = 506)				AC Patients (n = 510)			
	Grade (%)				Grade (%)			
Adverse Event*	1	2	3	4	1	2	3	4
Hematologic								
Anemia	3	2	< 1	< 1	4	3	1	< 1
Neutropenia	< 1	1	10	51	1	2	12	43
Thrombocytopenia	< 1	< 1	0	< 1	< 1	< 1	1	0
Nonhematologic								
Asthenia	43	32	3	< 1	42	31	4	< 1
Edema	27	7	< 1	0	17	3	< 1	< 1
Fever	14	5	3	2	11	4	2	< 1
Infection	8	4	7	< 1	7	5	8	< 1
Myalgia	22	10	1	< 1	11	5	< 1	< 1
Nausea	38	13	2	< 1	43	32	7	< 1
Phlebitis	8	3	< 1	0	1	1	0	0
Stomatitis	23	10	< 1	< 1	29	15	1	1
Vomiting	9	5	< 1	< 1	21	16	5	< 1

Abbreviations: AC, doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide.
*Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) term.

our exploratory analysis of DFS in major subgroups (Fig 3) suggests that it is more active than AC regardless of age, nodal status, or receptor status.

The following question arises: When would we use TC rather than AC? There are many patients for whom four cycles of AC are still reasonable treatment, such as those who are node negative, low-level node positive, particularly ER positive, but AC puts these patients at risk of cardiotoxicity. For these patients, who were studied in this trial, TC seems to be an ideal regimen. Patients who present with significant heart disease or prior anthracycline therapy (eg, prior breast cancer) are also candidates. Finally, although not formally studied, TC seems to be an ideal adjuvant regimen to study in combination with trastuzumab in *HER2*-overexpressing cancers because of its lack of cardiotoxicity.[13,16]

Thirty-one years ago, the original AC regimen was reported.[17] Now, there is a superior nonanthracycline regimen, TC.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. 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.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
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ERRATUM

The December 1, 2006, article by Jones et al, entitled "Phase III Trial Comparing Doxorubicin Plus Cyclophosphamide With Docetaxel Plus Cyclophosphamide As Adjuvant Therapy for Operable Breast Cancer," (J Clin Oncol 24:5381-5387, 2006) requires clarification.

In the Patients and Methods section, under Study Design, the second sentence was given as:

"Patients were randomly assigned to four cycles of either standard-dose AC (60 and 600 mg/m^2, respectively) or TC (75 and 600 mg/m^2, respectively) administered by intravenous **bolus** on day 1 of each 21-day cycle for four cycles as adjuvant treatment after complete surgical excision of the primary tumor (Fig 1)."

Whereas it should have read:

"Patients were randomly assigned to four cycles of either standard-dose AC (60 and 600 mg/m^2, respectively) or TC (75 and 600 mg/m^2, respectively) administered by intravenous **infusion over 30 to 60 minutes** on day 1 of each 21-day cycle for four cycles as adjuvant treatment after complete surgical excision of the primary tumor (Fig 1)."

In the Patients and Methods section, under Treatment, the fourth sentence was given as:

"AC (60 and 600 mg/m^2, respectively) or TC (75 and 600 mg/m^2, respectively) was administered by intravenous **bolus** on day 1 of each 21-day cycle."

Whereas it should have read:

"AC (60 and 600 mg/m^2, respectively) or TC (75 and 600 mg/m^2, respectively) was administered by intravenous **infusion over 30 to 60 minutes** on day 1 of each 21-day cycle."

The online version has been corrected in departure from the print.

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