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ORIGINAL REPORT

Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735

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ABSTRACT

Purpose
We previously reported that four cycles of docetaxel/cyclophosphamide (TC) produced superior disease-free survival (DFS) compared with four cycles of doxorubicin/cyclophosphamide (AC) in early breast cancer. Older women are under-represented in adjuvant chemotherapy trials. In our trial 16% of patients were ≥ 65 years. We now report 7-year results for DFS and overall survival (OS) as well as the impact of age, hormone receptor status, and *HER2* status on outcome and toxicity.

Patients and Methods
Patients were randomly assigned to receive either four cycles of standard-dose AC (60/600 mg/m^2; n = 510), or TC (75/600 mg/m^2; n = 506), administered by intravenous infusion every 3 weeks.

Results
The median age in women younger than 65, was 50 years (range, 27 to 64) and for women ≥ 65 was 69 years (range, 65 to 77). Baseline characteristics in the two age subgroups were generally well matched, except that older women tended to have more lymph node involvement. At a median of 7 years follow-up, the difference in DFS between TC and AC was significant (81% TC *v* 75% AC; *P* = .033; hazard ratio [HR], 0.74; 95% CI 0.56 to 0.98) as was OS (87% TC *v* 82% AC; *P* = .032; HR, 0.69; 95% CI, 0.50 to 0.97). TC was superior in older patients as well as younger patients. There was no interaction of hormone-receptor status or HER-2 status and treatment. Older women experienced more febrile neutropenia with TC and more anemia with AC.

Conclusion
With longer follow-up, four cycles of TC was superior to standard AC (DFS and OS) and was a tolerable regimen in both older and younger patients.

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INTRODUCTION

We previously reported in this *Journal* the 5-year results of US Oncology Research's first trial of adjuvant chemotherapy for early breast cancer (US Oncology Trial 9735).[1] Among 1,016 patients with operable breast cancer, the nonanthracycline regimen of docetaxel plus cyclophosphamide (TC) given for four cycles was superior to standard doxorubicin and cyclophosphamide (AC) for the primary end point of disease-free survival (DFS); at 5 years the DFS associated with TC was 86% versus 80% for AC (hazard ratio [HR], 0.67; *P* = .015) with a trend in overall survival favoring TC (90% *v* 87%; HR, 0.76; *P* = .13). Toxicity assessment showed more edema, myalgia, arthralgia, and febrile neutropenia with TC and more nausea and vomiting with AC.

In another recent publication, the Cancer and Leukemia Group B[2] reported that older women were under-represented in four of their major node-positive adjuvant studies with only 7% of patients in these trials being 65 years or older. In our AC/TC trial, 16% of patients entered were 65 or older, which provided the opportunity, with longer follow-up (median, 7 years), to examine the effect of older age

on outcome and toxicity. In addition, this analysis allowed us to evaluate outcomes in relation to *HER2* status for women who had paraffin blocks available for testing.[3]

PATIENTS AND METHODS

Eligibility

In order to be eligible for enrollment, patients age 18 to 75 years had to have Karnofsky PS ≥ 80%, and no evidence of metastatic disease.[1] Before receiving study treatment, patients must have had complete surgical excision of the primary tumor (a lumpectomy and axillary dissection or modified radical mastectomy). No previous neoadjuvant chemotherapy was permitted. Primary tumor size must have been ≥ 1.0 cm and smaller than 7.0 cm. Subjects were required to have the following laboratory values: absolute neutrophil count (ANC) of ≥ 1,400/mm^3, platelet count of ≥ 100,000/mm^3, hemoglobin of ≥ 9 g/dL, direct bilirubin of ≤ 1.5 mg/dL, serum creatinine lower than 1.5 mg/dL, and AST ≤ 2.5× upper limit of normal. Subjects who had active serious infection or any underlying medical condition, or those who had received any prior chemotherapy or hormone therapy for the current disease, were excluded. Pregnant/lactating women were prohibited from participating in this study.

Study Design

This was a randomized, prospective, phase III study comparing four cycles of either AC or TC as adjuvant chemotherapy in women with operable stage I-III invasive breast cancer.

Chemotherapy was administered before radiation therapy (XRT), if XRT was indicated (for breast conservation or postoperative XRT for patients with four or more involved axillary lymph nodes). After completing four cycles of chemotherapy (±XRT), all patients with hormone receptor–positive breast cancer received tamoxifen for 5 years. The protocol was approved by a central institutional review board with jurisdiction over specific sites that registered patients on study, and all patients were required to sign an informed consent form before being enrolled into the study.

Treatment

Patients received four cycles of therapy, administered every 3 weeks, as either AC or TC. Treatment was discontinued if the patient experienced progressive disease or unacceptable toxicity. Dexamethasone 8 mg orally twice daily for five doses starting 1 day before each infusion was given to patients receiving TC. The chemotherapy regimens AC (60/600 mg/m^2) or TC (75/600 mg/m^2) were administered by intravenous (IV) infusion on day 1 in each cycle.[1] Prophylactic quinolone antibiotics were recommended but not required. Details concerning the treatment plan and dose modifications have been previously published.[1]

Assessments and Criteria for Assessing Toxicity

Assessments of toxicity were done at every clinic visit: assessments of disease were done at regularly scheduled intervals throughout the study and have been reported in a prior publication.[1]

Specifics for assessing toxicity have been reported.[1] Toxicities were graded using the National Cancer Institute Common Toxicity Criteria (version 1).

HER2 Status

Under the direction of Drs John Pippen, Dan Mackey, and Stefan Riedel, paraffin tissue blocks were obtained from 170 patients, with an emphasis on those patients who had relapsed as of December 2005 as well as cases available at Baylor University Medical Center (Dallas, TX), the primary hospital for several of the coauthors.

Before performing the fluorescent in situ hybridization (FISH) procedure, the presence of carcinoma was confirmed by hematoxylin and eosin stain of the selected slides/tissue blocks. *HER2* status was then assessed by FISH using the PathVysion kit (Vysis; Abbott Laboratories. Abbott Park, IL). The *HER2/neu* gene number was determined using the PathVysion kit containing a mixture of SpectrumOrange-labeled *HER2/neu* gene and SpectrumGreen-labeled centromere region on chromosome 17. Slides were reviewed using a fluorescent microscope, and FISH scoring was performed by counting fluorescent signals in 50 malignant, non-overlapping cell nuclei. The ratio of *HER2/neu* gene signals and to chromosome 17 centromere signals was calculated. A standard cutoff for this gene ratio of ≥ 2.0 was selected as the definition of positive according to the manufacturers guidelines. Polysomy c17 was not considered. Hormone receptor status (ER/PR) was obtained from pathology reports by various laboratories used by sites within the network.

Statistical Analysis

Details of the statistical analysis of the entire study have been previously published.[1]

The primary objective of this analysis was to compare disease-free survival (DFS) and overall survival (OS) of AC versus TC in early operable breast cancer at a median follow-up of 7 years. Two additional unplanned substudies were undertaken and the results are presented in this article. Secondary objectives of this analysis were: to determine outcome in DFS by age (< 65 *v* ≥ 65) and treatment regimen, to assess the impact of HER2 status on DFS, to determine toxicity profiles by age and treatment regimen, and to compare DFS of estrogen receptor (ER)/progesterone receptor (PR)–positive patients versus ER/PR–negative patients. For these secondary objectives (age, HER2 status, and hormone receptor status), only DFS analyses are shown (due to small sample size) and hazard ratios are reported without *P* values, but are shown in a Forest plot.

DFS was calculated as the time from the first dose of chemotherapy until the date of any recurrence of breast cancer (local or distant), a new second breast cancer or any other type of cancer, death due to any cause without relapse or recurrence of breast cancer, or the date of last patient contact. Survival was calculated as the time from the first dose of chemotherapy to the date of death (any cause) or to the date of last contact. The database was locked October 2007. DFS and OS were assessed using Kaplan- Meier method[4] and log-rank tests were utilized to compare the differences between curves. For purposes of illustration, absolute percent differences are given for the different curves at 7 years. In addition, to further explore the prognostic effect of study arm on DFS and OS, both univariate (including study arm only as independent variable) and multivariate (including other baseline variables such as age, tumor size, and number of positive nodes, in addition to study arm) Cox regression models were constructed. The differences in toxicities between the two treatment arms and the two age groups were tested using χ^2 statistics. Treatment-related toxicities by age group were reported using Coding Symbols for Thesaurus of Adverse Reaction Terms and summarized by highest grade/patient.

All statistical analyses were done using SAS version 8 (SAS Institute, Cary, NC) and Statistica software (Statsoft, Tulsa, OK, 1995; StatSoft version 6.1, Tulsa, OK). Survival (DFS, OS) and demography was run using the intention-to-treat population, all patients receiving at least one dose (the safety population) were used for the calculation of toxicity.

RESULTS

Patient Characteristics

A total of 1,016 subjects with operable stage I to III invasive breast cancer were enrolled between July 1, 1997, and January 5, 2000. Patient demographics for the entire patient population have been previously reported.[1] Disease characteristics by age (< 65 *v* ≥ 65) have not been previously reported and are summarized in Table 1. Among older women there were more women entered with higher-risk cancer (ie, involved axillary nodes, particularly four or more lymph nodes involved). For example, among women in the ≥ 65 group, 19% on TC and 16% AC had four or more nodes involved compared with 10% and 9%, respectively in the younger cohorts (age < 65).

Table 1. Baseline Demographics by Age Group

	Age by Arm (years)											
	< 65				≥ 65				All Patients			
	TC		AC		TC		AC		TC		AC	
Demographic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	428		428		78		82		506		510	
ER+ and/or PR+	312	73	291	68	56	72	60	73	368	73	351	69
PR−/PR−	115	27	136	32	22	28	21	26	137	27	157	31
Unknown	1		1		1		0		2		1	
Node												
0	212	50	217	51	28	36	31	38	240	48	248	49
1 to 3	174	41	174	41	35	45	38	46	209	41	212	42
4+	42	10	37	9	15	19	13	16	57	11	50	9
Median age, years	50		49		69		68		52		51	
Range	27-64		27-64		65-77		65-77		27-77		27-77	

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

DFS

At a median of 7-years of follow-up, the number of events and deaths used in calculations of DFS and OS are summarized in Table 2. DFS, by treatment, is shown in Figure 1A. At 7 years there remains a 6% difference favoring TC (HR, 0.74; 95% CI, 0.56 to 0.98; $P = .033$). DFS by age and treatment arm is shown in Figure 1B and Forest plots for the hazard ratios of age, *HER2*, and ER status are summarized in Figure 2. In these small subgroups, TC was associated with more favorable DFS compared with AC in both younger and older women. Among the 170 patients whose cancers were assessed for *HER2* status, 5-year DFS was worse for the 46 patients (27%) with *HER2*-positive disease compared with the 124 patients (73%) with *HER2*-negative tumors (44% for AC HER2 positive *v* AC 65% *HER2* negative; 56% for TC *HER2*+ *v* 76% TC *HER2* negative). In both *HER2* groups (negative and positive), TC was favored over AC regardless of *HER2* status (Figs 3A and 3B); the HRs are summarized in Figure 2.

Table 2. Events Used for Disease-Free Survival and Overall Survival Calculations

	TC		AC	
Event	No.	%	No.	%
No. of patients	506		510	
No. of events (relapse or recurrence, 2nd cancer(s), and death without relapse or recurrence)	88		118	
Relapse of breast cancer	75	85	90	76
Death from all causes	58	100	84	100
Death without relapse	13	22	25	30
Myocardial infarction	0		1	
Myelofibrosis	0		1	
Myelodysplastic syndrome	0		1	
Coronary artery disease	0		1	
Cerebral vascular accident	0		3	
Congestive heart failure	0		1	
Gastric/cervical cancer	0		2	
Suicide	0		1	
Debility	0		1	
Respiratory failure	1		1	
Cardiac arrest	2		1	
Ovarian/lung cancer	2		0	
Auto accident	2		0	
Unknown (no autopsy performed)	6		11	
Relapsed patients, death not due to breast cancer	15	26	16	19
Deaths due to breast cancer	30	52	43	51

Abbreviations: TC, docetaxel/cyclophosphamide; AC, doxorubicin/cyclophosphamide.

OS

OS by treatment is shown in Figure 1C. A significant difference in OS now exists at 7 years for TC over AC (HR, 0.69; 95% CI, 0.50 to 0.97; $P = .032$). Survival by age and regimen is shown in Figure 1D. TC is favored over AC in both the older as well as younger patients. Due to the larger numbers of deaths without recurrence, the older patients had worse OS.

As expected, there were more deaths without recurrence in older women (19 of 160; 12%) as compared with younger women (19 of 856; 2%; $P < .01$). These deaths were attributed to a large number of noncancer causes commonly seen in an older population. Causes of death without relapse are summarized in Table 2.

For univariate analysis, Cox regression model was implemented including only study arm for both OS and DFS. TC showed beneficial effect over AC for both OS (HR, 0.69; 95% CI, 0.50 to 0.97) and DFS (HR, 0.74; 95% CI, 0.56 to 0.98).

For multivariate analysis, Cox regression models were constructed for OS and DFS, respectively, and both took, in addition to study arm, other variables including age, tumor size, and number of positive nodes into consideration to explore their relationship with OS and DFS rates. Both models indicated hazardous effect of older age (OS: HR, 2.07; 95% CI, 1.44 to 2.99; DFS: HR, 1.51; 95% CI, 1.09 to 2.09), larger tumor size (OS: HR, 1.46; 95% CI, 1.10 to 1.94; DFS: HR, 1.43; 95% CI, 1.13 to 1.81), and larger number of positive nodes (OS: HR, 1.60; 95% CI, 1.26 to 2.03; DFS: HR, 1.50; 95% CI, 1.23 to 1.83). However, the models again showed beneficial effect of TC over AC (OS: HR, 0.70; 95% CI, 0.50 to 0.98; DFS: HR, 0.75; 95% CI, 0.57 to 0.99).

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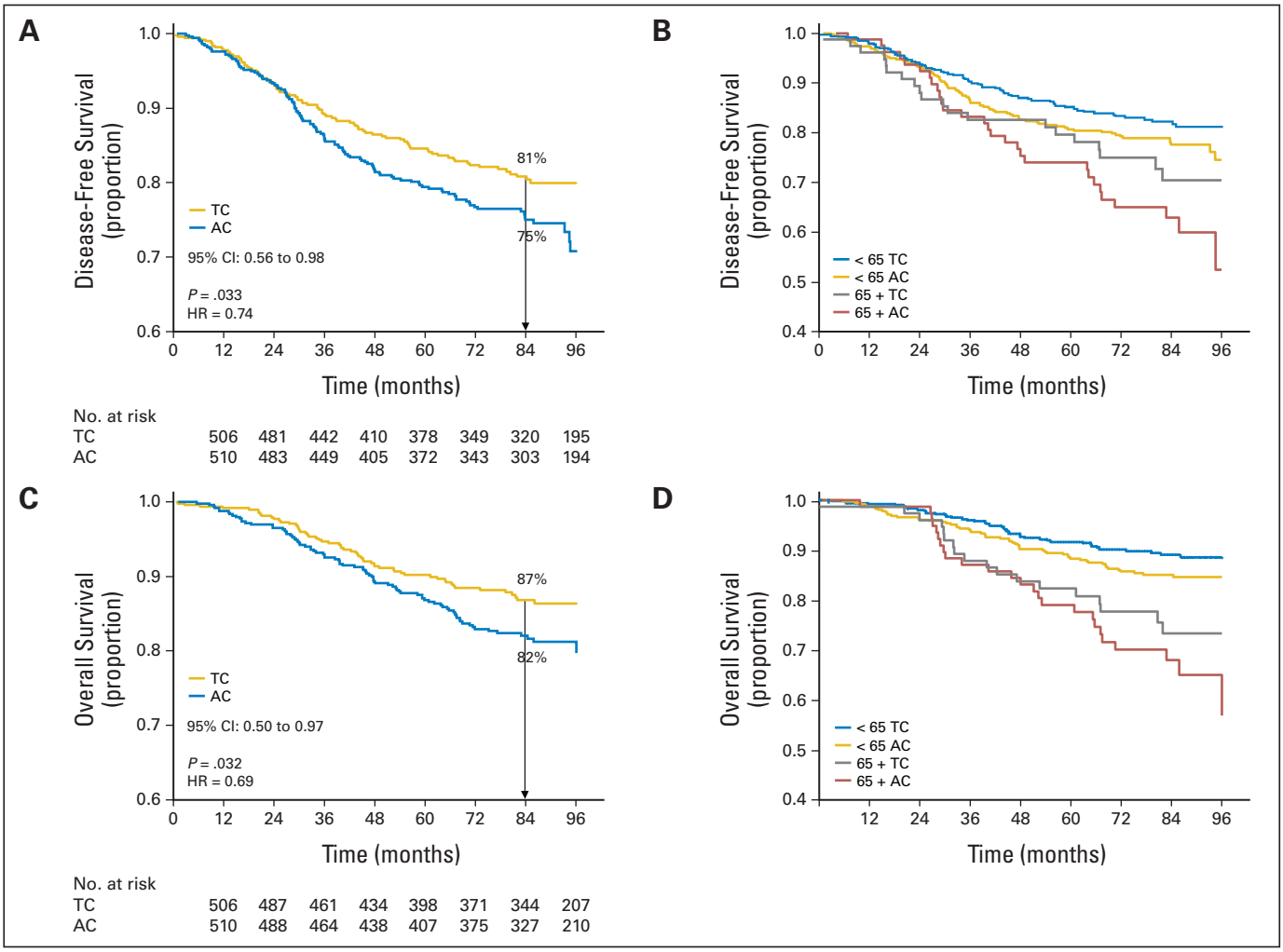

Fig 1. Disease-free survival (DFS) and overall survival (OS) (A) DFS by treatment; (B) DFS by treatment and age; (C) OS by treatment: 1 day; (D) OS by treatment and age. TC, docetaxel/cyclophosphamide; AC, doxorubicin/cyclophosphamide.

Toxicity

Using the cutoff of age 65 years, we compared grade 3 and 4 adverse events by treatment for hematologic and nonhematologic events occurring during or within 30 days of completing chemotherapy (Table 3). Almost all of the grade 3 to 4 anemia occurred in older women receiving AC (5% $v \leq 1\%$ in other groups). Febrile neutropenia (fever $\geq 38.5°C$ with neutropenia) was previously reported as 5% with TC and 2.5% with AC.[2] When this was reanalyzed by age, the rates of febrile neutropenia were doubled in the older patients: for TC, 8% for older and 4% for younger patients compared with 4% in older and 2% in younger AC patients. Of note, these rates of febrile neutropenia reflect the widespread use of prophylactic antibiotics during

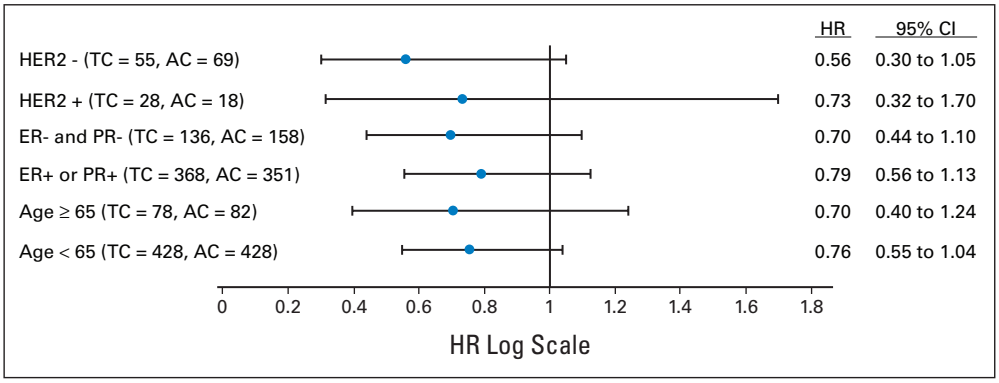

Fig 2. Summary of unplanned, exploratory analyses of disease-free survival hazard ratios (HR) and CI. Docetaxel/cyclophosphamide (TC) is favored left of 1. AC, doxorubicin/cyclophosphamide; ER, estrogen receptor; PR, progesterone receptor.

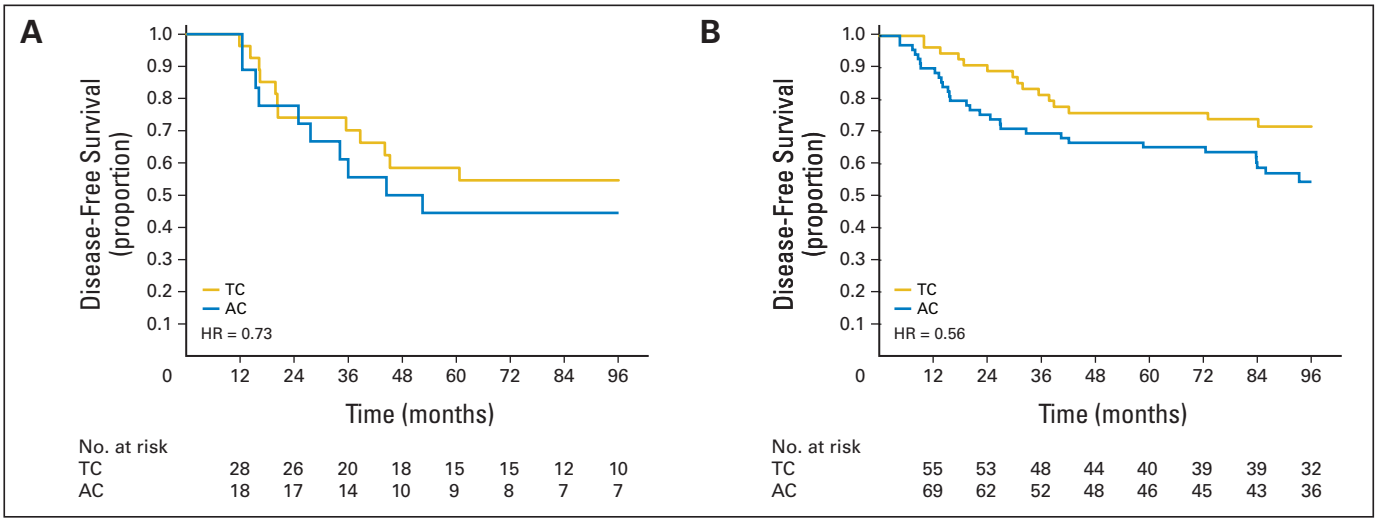

Fig 3. Disease-free survival (DFS) by HER2 status (A) DFS by treatment in HER2-positive disease; (B) DFS by treatment in HER2-negative disease. TC, docetaxel/cyclophosphamide; AC, doxorubicin/cyclophosphamide.

hematologic nadirs during the conduct of this trial (1997 to 2000). Use of prophylactic granulocyte colony-stimulating factor to stimulate neutrophil production was not utilized in this study.

There were three late deaths without relapse, probably related to treatment, and all occurred in the AC group: a 45-year-old woman died of cardiomyopathy and congestive heart failure, and two older women died of complications related to myelodysplasia and myelofibrosis, respectively. One more patient died of acute leukemia 10 years after AC.

Table 3. Grade 3-4 Toxicities by Age Group

Toxicity	% by Age Group			
	< 65		≥ 65	
	TC (n = 428)	AC (n = 428)	TC (n = 78)	AC (n = 82)
Hematologic				
Anemia	< 1	1	< 1	5
Neutropenia	60	54	52	59
Thrombocytopenia	< 1	1	0	< 1
Febrile neutropenia	4	2	8	4
Nonhematologic				
Asthenia	3	4	6	9
Edema	1	< 1	0	< 1
Fever	4	3	6	4
Infection	7	10	6	2
Myalgia	2	1	0	< 1
Arthralgia	1	1	< 1	< 1
Stomatitis	1	2	0	< 1
Diarrhea	2	1	5	1
Nausea	2	7	3	5
Vomiting	1	6	0	0
Phlebitis	< 1	< 1	< 1	0

Abbreviations: TC, docetaxel/cyclophosphamide; AC, doxorubicin/cyclophosphamide.

DISCUSSION

Almost all of the major adjuvant regimens that are considered improvements over four cycles of standard AC have added a taxane either to AC[5] or have given a taxane after AC, thus preserving the anthracycline backbone of the regimen.[5-10] At present, to our knowledge, this is the only trial to evaluate the substitution of docetaxel for doxorubicin thus creating a modern nonanthracycline combination for adjuvant therapy. At 5 years, this trial showed a significant DFS benefit for TC,[1] but now with longer follow-up shows a significant benefit for OS as well.

In this trial, half of the younger patients (compared with 36% of older patients) had node-negative disease. Overall, 48% of all patients had node-negative disease and 41% had one to three positive nodes. Only approximately 10% of younger patients had four or more nodes involved compared with 17.5% of older patients. However, as we reported previously[1] the relative risk reductions for node-negative disease and those with nodal involvement were similar. These data cannot be generalized to those with four or more positive lymph nodes given the small number of women in this subset.

Muss et al[2] reported that only 7% of women in four of their largest node-positive adjuvant breast cancer trials were 65 years or older, but that these older patients derived similar benefit with more aggressive treatment regimens as younger patients. Toxicity was greater in these older women but in general treatment was well tolerated. Our data show that older women tolerated treatment well (Table 3). Even among older women, the rate of febrile neutropenia is still far below the 17% to 20% rate suggested by the American Society of Clinical Oncology to consider routine WBC growth factor prophylaxis.[11] We recommended prophylactic oral antibiotics in this study, which may have minimized this toxicity; however, we do not know the precise number of patients who received antibiotics prophylactically. Although there are higher rates of febrile neutropenia with TC, it proved to be better tolerated than AC regardless of age (Figs 2A and 2B; Table 2). Almost all grade 3 to 4 anemia occurred in older patients

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receiving AC and in this trial most of the patients with more severe anemia were transfused. The higher rate of severe anemia seen with AC in this trial is consistent with the known bone marrow toxicity of anthracyclines and the increased risk of bone marrow damage (leukemia or myelodysplasia).[12] In fact, two older women in this trial died from myelodysplasia and myelofibrosis, respectively. No patient in the TC treatment arm had a similar outcome. The higher rates of anemia in older women, as well as the late apparent marrow toxicities, argue for the increased use of TC over AC in older women to avoid anthracyclines. Leukemia and myelodysplasia are major anthracycline related toxicities in women with breast cancer treated with anthracyclines and another reason for considering nonanthracycline regimens.[2,13,14] Because there were only two cases no attempt was made to look for the use of adjuvant radiation therapy as a contributing factor.

Anthracycline cardiac toxicity is well defined,[15-17] and one patient on the AC arm died of cardiomyopathy and congestive heart failure. Recent reports[18] provided data that suggest that older women receiving anthracycline-based adjuvant chemotherapy had much higher rates of CHF years after completing treatment, suggesting that we may well underestimate the impact of current anthracycline-containing regimens on long-term toxicities. This further supports the selection of TC as a nonanthracyline-based regimen for women with node-negative and lower-risk, node-positive breast cancer.

In this trial, TC was equally effective in hormone receptor–positive disease as well as receptor-negative disease (Fig 2).[1] In several trials taxanes have been more effective in receptor negative, compared with the receptor positive patients.[9,19] Recently, Hayes et al[20] in a retrospective analysis showed no benefit from paclitaxel when added to AC in patients with *HER-2* negative, node-positive estrogen receptor–positive breast cancer. A recent meta-analysis however showed benefit for taxanes in this setting.[21] Our trial is now one of three utilizing docetaxel where the benefit of the taxane regiment is equally apparent in receptor positive and receptor negative disease.[5,6] Whether this is due to the choice of docetaxel over paclitaxel or some other factor such as schedule remains unknown. Finally, in an exploratory analysis (Figs 2, 3A, and 3B) TC was equally effective in *HER2*-positive and *HER2*-negative disease, a result consistent with what was observed in the BCIRG 001 trial and a recent meta-analysis.[5]

The benefits of anthracyclines have been shown to be greater in patients with tumors with *HER2* overexpression.[22] A recent meta-analysis[23] confirms that sensitivity to anthracyclines occurs only in the 20% to 25% of patients with *HER2*-positive tumors. Recently this concept has been challenged as it appears that the main target of anthracyclines is topoisomerase IIa (TOPO2A). This gene is on the same amplicon as the *HER2* gene on chromosome 17q21 and it is overexpressed in one third of patients with *HER2*-positive disease and rarely in *HER2*-negative disease.[24,25] In some of the same trials where anthracycline sensitivity was related to *HER2* overexpression, it now appears that it may be TOPO2A overexpression (the target for anthracyclines) that is responsible.[26] This controversy has been discussed recently by Pritchard et al[27] If all or most of anthracycline sensitivity resides in TOPO2A overexpression and that this occurs primarily in *HER2*-positive disease, the implication is that there may be little if any benefit to anthracyclines in *HER2*-negative breast cancer.[25]

Further research is needed to determine if anthracyclines are necessary in the adjuvant setting. To test the hypothesis that anthracyclines may be safely omitted in *HER2*-negative early-stage breast cancer, US Oncology Research has embarked on a pivotal randomized phase III trial comparing six cycles of treatment with either TC or the three-drug regimen of docetaxel, doxorubicin, and cyclophosphamide in 2,000 *HER2*-negative patients. Tissue will be examined for the presence of the *TOPO2A* gene or protein expression and proliferation. This trial should definitively resolve whether anthracycline regimens should remain major choices for adjuvant therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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