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Long-term outcomes after adjuvant treatment of sequential versus combination docetaxel with doxorubicin and cyclophosphamide in node-positive breast cancer: BCIRG-005 randomized trial

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Background: The optimal regimen for adjuvant breast cancer chemotherapy is undefined. We compared sequential to concurrent combination of doxorubicin and cyclophosphamide with docetaxel chemotherapy in women with node-positive non-metastatic breast cancer. We report the final, 10-year analysis of disease-free survival (DFS), overall survival (OS), and long-term safety.

Patients and methods: A total of 3298 women with HER2 nonamplified breast cancer were randomized to doxorubicin and cyclophosphamide every 3 weeks for four cycles followed by docetaxel (AC → T) every 3 weeks for four cycles or docetaxel, doxorubicin, and cyclophosphamide (TAC) every 3 weeks for six cycles. The patients received standard radiotherapy and endocrine therapy and were followed up for 10 years with annual clinical evaluation and mammography.

Results: The 10-year DFS rates were 66.5% in the AC → T arm and 66.3% in the TAC arm ($P = 0.749$). OS was 79.9% in the AC → T arm and 78.9% in the TAC arm ($P = 0.506$). TAC was associated with higher rates of febrile neutropenia, although G-CSF primary prophylaxis greatly reduced this risk. AC → T was associated with a higher rate of myalgia, hand-foot syndrome, fluid retention, and sensory neuropathy.

Conclusion: This 10-year analysis of the BCIRG-005 trial confirmed that the efficacy of TAC was not superior to AC → T in women with node-positive early breast cancer. The toxicity profiles differ between arms and were consistent with previous reports. The TAC regimen with G-CSF support provides shorter adjuvant treatment duration with less toxicity.

Trial Registration: ClinicalTrials.gov Identifier NCT00312208.

Key words: early stage breast cancer, adjuvant chemotherapy, doxorubicin, docetaxel, cyclophosphamide

introduction

Adjuvant taxane chemotherapy given to women with early breast cancer provides relapse-free and overall survival (OS) advantages when compared with non-taxane regimens [1]. Unlike paclitaxel, docetaxel can be administered concurrently with anthracyclines without prohibitive cardiotoxicity, and the relative merits of sequential anthracycline–docetaxel regimens and concurrent anthracycline–docetaxel regimens [2–5] were unclear at the time this study was designed.

The concurrent regimen chosen for study was the TAC regimen, which had shown advantages both in terms of disease-free survival

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(DFS) and OS over a non-taxane adjuvant regimen in the BCIRG-001 study [6]. The patients in the TAC arm (docetaxel, doxorubicin, and cyclophosphamide) had a 10-year DFS of 62%, compared with 55% for patients who received FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) ($P = 0.004$) and corresponded to a 20% relative reduction in the risk of relapse. Similarly, patients who received TAC experienced superior survival at 10 years (76% compared with 69% for patients in the FAC group, $P = 0.002$) and corresponded to a 26% relative reduction in the risk of death. This superiority of TAC over FAC was seen in all planned subgroups analyses, including the number of lymph nodes, hormone receptor status, and HER2 status [6].

To better characterize the efficacy and safety of the sequential versus concurrent use of a docetaxel–anthracycline based regimen, we launched the BCIRG-005 study. This phase III trial compared the concomitant combination of doxorubicin, cyclophosphamide, and docetaxel (TAC) with a sequential combination of doxorubicin and cyclophosphamide followed by docetaxel monotherapy (AC → T) in women with HER2-negative, node-positive early breast cancer. A total of 3298 patients were enrolled between August 2000 and February 2003. The primary end point was DFS and secondary end points included OS and safety. The main analysis was conducted at 65 months median follow-up and was previously reported [7]. We now present the results of the final analysis at 10 years of follow-up.

patients and methods

patients, patient characteristics, and study design

As previously reported, eligible subjects were women between 18 and 70 years of age with operable, HER2-nonamplified, invasive adenocarcinoma of the breast (T1-3, clinically N0-1, M0); normal cardiac and adequate hematological, renal, and hepatic function [7]. Definitive surgical treatment was required and margins of the resected specimen had to be histologically free of disease, and at least one positive node from axillary dissection was required. Criteria for exclusion included advanced or bilateral disease, prior radiation or systemic anticancer therapy for breast cancer, prior anthracycline or taxane therapy, pregnancy, lactation, and any serious illness or medical condition other than breast cancer.

In this phase III, multicenter, prospective trial, patients were randomized to chemotherapy regimen after stratification for institution, hormonal receptor status (local laboratory estrogen and/or progesterone receptor positive versus negative), and number of involved axillary lymph nodes per patient (one to three versus four or more).

All chemotherapeutic agents were administered intravenously in standard doses and schedules as previously reported [5, 6]. The patients in the AC → T arm received doxorubicin (60 mg/m^2) over 15 min and cyclophosphamide (600 mg/m^2) over 5–60 min on Day 1 every 3 weeks for four cycles, followed by four cycles of docetaxel (100 mg/m^2) over 1 h every 3 weeks. In the TAC arm, chemotherapy consisted of six cycles of doxorubicin (50 mg/m^2), cyclophosphamide (500 mg/m^2), and docetaxel (75 mg/m^2), infused in this order every 3 weeks.

In both arms, steroid premedication was given for 3 days, starting the day before the administration of docetaxel. Oral antibiotic prophylaxis was mandatory in the TAC arm but permitted in the AC → T arm only after a grade 3 or 4 infection. Granulocyte colony-stimulating factor (G-CSF) could be used for primary prophylaxis in either arm at the discretion of the investigator and was suggested for the treatment of febrile neutropenia and as prophylaxis after an episode of febrile neutropenia, infection, or for inadequate neutrophil recovery on Day 21.

Doses were reduced according to standard toxicity criteria and treatment was discontinued in cases of severe or unacceptable toxicity (despite adequate dose reduction and con-medication); chemotherapy delays exceeding 2 weeks as a result of drug-related toxicities; withdrawal of consent; or breast cancer relapse or second primary malignancy (other than non-melanoma skin cancer, or *in situ* carcinoma of the uterine cervix or breast).

On completion of chemotherapy, patients with hormone receptor-positive disease received adjuvant endocrine therapy. Radiation therapy was mandatory after breast-conserving surgery and post-mastectomy nodal or boost radiation was given according to each institution's guidelines.

Regional and/or institutional ethics committees of all participating institutions provided ethical approval of the study. All patients provided written informed consent, and the trial was conducted according to good clinical practice and the Declaration of Helsinki. Study conduct and data analysis were supervised by an independent data monitoring committee.

The study overview is available in the CONSORT diagram (supplementary Figure S1, available at *Annals of Oncology* online).

measurement of efficacy/safety end points and statistical methods

Baseline assessments were previously described [7] and included normal left ventricular ejection fraction (LVEF) by echocardiography or MUGA scanning. After completion of chemotherapy, the patients were followed up in clinic every 3 months for the first 2 years, every 6 months in years 3–5, and annually in years 6–10. There were no protocol mandated cardiac evaluations after baseline.

The full statistical plan was previously published [7]. This final analysis was triggered by 10 years of follow-up in surviving patients and was conducted according to the intention-to-treat (ITT) principle. The efficacy population consists of all randomized patients. The primary end point was DFS, defined as the time from randomization to the earliest date of a clinical relapse, a second cancer (with the exception of skin cancer other than melanoma, carcinoma *in situ* of the breast, or cervix), or death.

Secondary end points included safety and OS, defined as the time from randomization until death from any cause. Unadjusted analyses and analyses according to the Cox proportional-hazards model (adjusted for age, tumor size, nodal status, hormone-receptor status) were carried out to estimate hazard ratios and 95% confidence intervals for DFS and OS. The Kaplan–Meier product limit methodology was used to analyze DFS and OS. The safety population consists of all treated patients and all safety analyses were conducted on an 'as-treated' basis. Adverse events were coded as per NCI-CTCAE version 2.0 criteria. All *P*-values reported are two-sided and all analyses were conducted by TRIO statisticians and carried out using the SAS statistical package (Version 9.0, SAS Institute, Cary, NC).

results

In 30 months, 335 centers in 37 countries randomized 3298 subjects. Baseline clinical characteristics were well-balanced between treatment arms, with a median age of 50 years (supplementary Table S1, available at *Annals of Oncology* online). In the AC → T arm, 90% of women received their full 8 cycles of chemotherapy, and 93% of women assigned TAC received their full 6 cycles of chemotherapy. The median relative dose intensity was 99% for all agents in both arms. Of those women with positive hormone receptors, 96% received adjuvant tamoxifen and/or aromatase inhibitors.

efficacy

At a median follow-up of 10.5 years, 1041 primary events had occurred, including 799 patients with breast cancer relapses,

185 s primary malignancies, and 651 deaths. The first observed DFS event in the IIT population and OS are summarized in Table 1. The estimated 10-year DFS rates were 66.5% in the AC → T arm and 66.3% in the TAC arm (Figure 1A, $P = 0.749$). Ten-year OS was 79.9% in the AC → T arm and 78.9% in the TAC arm (Figure 1B, $P = 0.506$). Subgroup analysis did not suggest differential efficacy in any population (supplementary Figure S2, available at *Annals of Oncology* online). In this HER2 nonamplified node-positive adjuvant population receiving aggressive therapy, the outcome of patients with hormone receptor-sensitive disease was significantly different from those with triple receptor negative disease (Figure 1C and D).

acute toxicities

The incidence of adverse events in the study BCIRG-005 was consistent with the known safety profiles of doxorubicin, cyclophosphamide, and docetaxel (Table 2). The acute toxicities of both regimens were manageable. A higher rate of febrile neutropenia was observed in TAC (17%) than was observed in AC → T (8%). However, in the 17% of patients who received primary prophylaxis with G-CSF beginning with the first cycle of TAC chemotherapy, the rate of febrile neutropenia was 9% (data not shown). The incidence of neutropenic infection was similar between the treatment arms. The G-CSF use was higher in the TAC arm (44% of patients; 33% of cycles) compared with the AC → T arm (28% of patients; 15% of cycles). G-CSF was started most often in the first or second cycle of TAC chemotherapy, while no such temporal pattern was seen in the AC → T group. While TAC was associated with more febrile neutropenia and thrombocytopenia, more grade 3 and 4 myalgia, hand-foot syndrome, sensory neuropathy, and fluid retention were observed in AC → T (respectively, 4.7%, 1.8%, 1.5% and 1.4%) compared with TAC (respectively, 0.9%, 0%, 0.2% and 0.6%).

hematologic malignancies

The overall incidence of leukemia was similar in both arms with four reported in patients who had received AC → T and five reported in patients who had received TAC. Three events of myelodysplastic syndrome were reported in patients who had received AC → T and one patient who had received TAC experienced a myelodysplastic syndrome. Leukemia and myelodysplastic syndrome were reported as the cause of death in two patients who received AC → T, and four patients who received TAC.

cardiac safety

The overall incidence of cardiac adverse events was similar in both arms. There was no reported occurrence of grade 4 or death due to CHF throughout the 10-year study duration. Left ventricular dysfunction was more frequently observed in the AC → T arm: any grade (19 versus 11 patients), grade 3/4 (6 versus 1 patient). Cardiac ischemia/infarction was more frequently observed in the TAC arm: any grade (10 versus 5 patients) and grade 3/4 (4 versus 0 patients). The most common cardiovascular serious adverse events were thrombosis/embolism and hypotension (Table 2).

Table 1. DFS and OS by intention to treat at 10 years post randomization

	AC → T ($n = 1649$)	TAC ($n = 1649$)
Patients without disease, *n* (%)	1131 (69%)	1126 (68%)
Patients with an event[a], *n* (%)	518 (31%)	523 (32%)
Breast cancer relapse	405 (25%)	394 (24%)
Distant recurrence	336 (20%)	332 (20%)
Local recurrence	71 (4.3%)	61 (3.7%)
Regional recurrence	44 (2.7%)	32 (1.9%)
Second primary cancer	87 (5.3%)	98 (5.9%)
Death NED	26 (1.6%)	31 (1.9%)
Stratified analysis		
Hazard ratio[b]	0.98	
95% CI	(0.87–1.11)	
P-value[c]	0.749	
Percent disease-free at		
Year 1	96.7%	97.2%
Year 2	91.4%	91.3%
Year 5	78.8%	79.3%
Year 10	66.5%	66.4%
Patients who died (*n*)	319	332
Patients alive (*n*)	1330	1317
Stratified analysis		
Hazard ratio[b]	0.95	
95%CI	(0.81–1.11)	
P-value[c]	0.506	
Percent event free at		
Year 1	99.3%	99.1%
Year 2	96.8%	96.5%
Year 5	88.9%	88.1%
Year 10	79.9%	78.9%

AC → T, doxorubicin plus cyclophosphamide, followed by docetaxel; TAC, doxorubicin, cyclophosphamide, and docetaxel; NED, no evidence of disease. Events are those included in the analysis of DFS.

[a]Earliest contributing event. A patient could be included in more than one event category; thus, the sum across rows may not equal the value in the 'Major' row. Most DFS events were distant relapses. Few deaths (AC → T: 26 and TAC: 31) were the first reported events experienced by the patients.

[b]AC → T Relative to TAC. Estimated using Cox regression stratified by the number of positive nodes and hormonal receptor status.

[c]Stratified log-rank *P*-value.

discussion

efficacy and acute toxicities

Adjuvant anthracyclines and taxanes are among the most active and commonly used cytotoxic chemotherapeutic agents for the treatment of early breast cancer. Several chemotherapy dosing regimens are commonly used, including concurrent, standard dose sequential, and dose dense sequential approaches. This 10-year analysis of the BCIRG-005 study shows that concurrent TAC was not superior in long-term DFS and OS effects to the sequential AC → T regimen. Both regimens had comparable efficacy across all stratification subgroups. Toxicity was manageable in both regimens, but more acceptable in the TAC regimen than AC → T therapy. Acute toxicities have not changed meaningfully

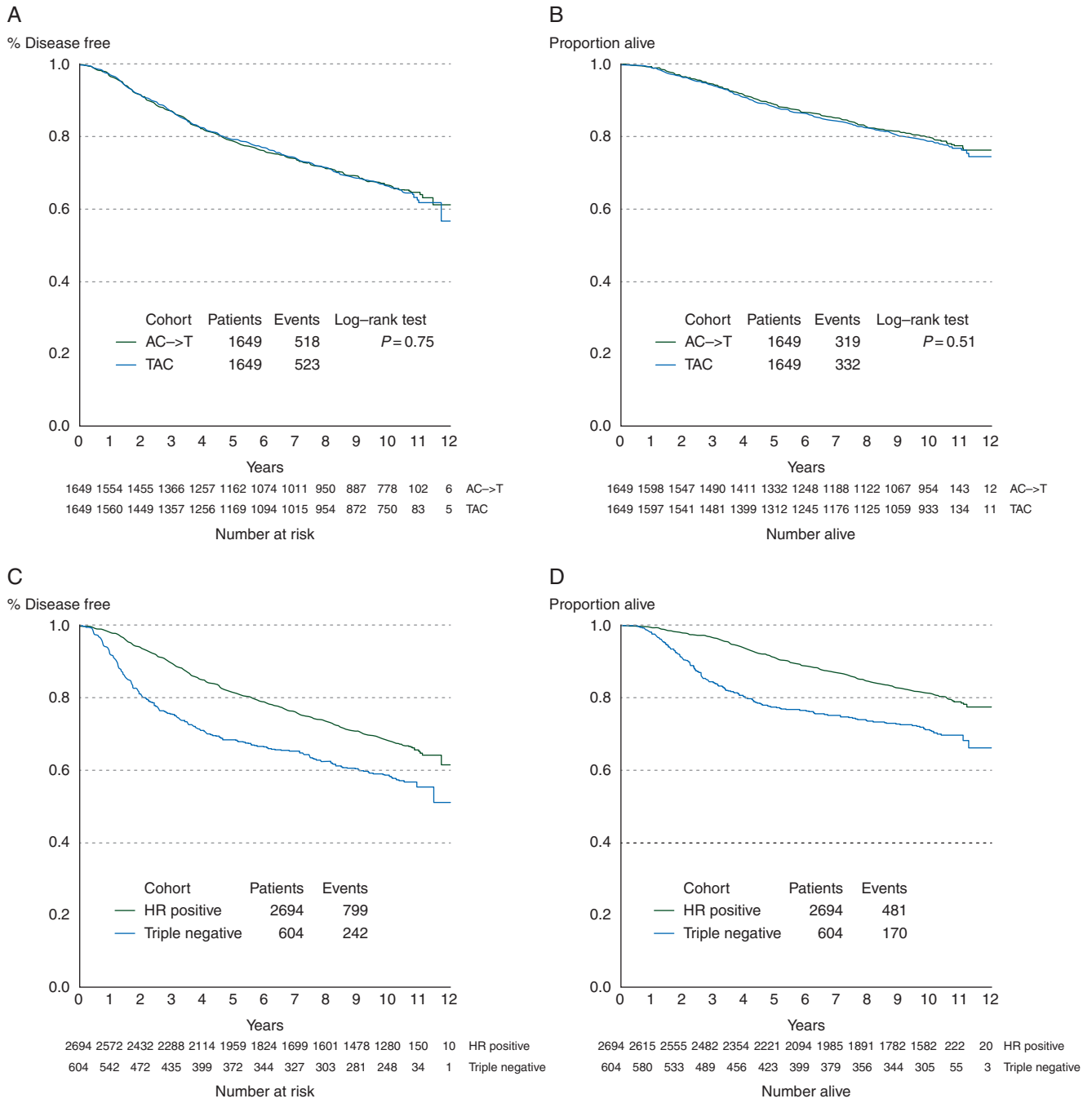

Figure 1. Kaplan–Meier curves of all patients. (A) Kaplan–Meier curves of DFS by treatment arm. The estimated 10-year DFS rates were 66.5% in the AC → T arm and 66.3% in the TAC arm ($P = 0.749$). (B) Kaplan–Meier curves of OS by treatment arm. The estimated 10-year OS rates were 79.9% in the AC → T arm and 78.9% in the TAC arm ($P = 0.506$). (C) Kaplan–Meier curves of DFS of hormonal receptor positive versus triple negative patient populations. The Kaplan–Meier estimates at 10 years are 58.5% for triple negative and 68.2% for hormone receptor positive patients (HR = 0.643, $P < 0.0001$). (D) Kaplan–Meier curves of OS of hormonal receptor positive versus triple negative patient populations. The Kaplan–Meier estimates at 10 years are 71.1% for triple negative and 81.3% for hormone receptor positive patients (HR = 0.558, $P < 0.0001$).

since the first report at a median follow-up of 56 months. We note that primary prophylaxis, used in 17% of TAC treated women, reduced the risk of febrile neutropenia to ~9%, and in accordance with ASCO guidelines, recommend that G-CSF prophylaxis be given to patients receiving TAC.

The available literature is insufficient to define a single, optimal chemotherapy regimen, due to the relative paucity of head-to-head comparisons among modern treatments. When placed in context of other published adjuvant therapies, it is clear that regimens of at least six cycles and that incorporate taxanes are more effective than regimens of fewer than six cycles or those without taxanes [1, 8]. While cross trial comparisons cannot be reliably made due to differences in eligibility criterion, intensity of toxicity assessment, durations of follow-up, and trial conduct, several direct comparisons of

Table 2. Grade 3/4 toxicities reported as adverse events within the safety population

Adverse event[a]	AC → T (n = 1634)	TAC (n = 1635)	P-value[b]
Hematologic toxicity and infection			
Neutropenia	946 (58%)	1003 (61%)	0.0459
Febrile neutropenia[c]	129 (8%)	283 (17%)	<0.0001
Infection			
Neutropenic infection	107 (7%)	135 (8%)	0.0711
Infection with unknown ANC	88 (5%)	55 (3%)	0.0048
Infection without neutropenia	32 (2%)	27 (2%)	0.5151
Anemia	30 (2%)	47 (3%)	0.0643
Thrombocytopenia	17 (1%)	35 (2%)	0.0167
Leukemia/myelodysplastic syndrome	7 (<1%)	6 (<1%)	0.7901
Nonhematologic toxicity			
Diarrhea	48 (3%)	35 (2%)	0.1503
Dyspnea	14 (<1%)	16 (<1%)	0.8549
Fatigue	101 (6%)	83 (5%)	0.1729
Fluid retention	23 (1%)	10 (<1%)	0.0236
Hand-foot skin reaction	30 (2%)	0 (0%)	<0.0001
Irregular menses	315 (19%)	301 (18%)	0.5315
Myalgia	77 (5%)	14 (<1%)	<0.0001
Sensory neuropathy	24 (1%)	4 (<1%)	<0.0001
Pain other than neuropathic	4 (<1%)	7 (<1%)	0.5481
Stomatitis	48 (3%)	42 (3%)	0.5238
Thrombosis/embolism	8 (<1%)	15 (<1%)	0.8499
Nausea	62 (4%)	71 (4%)	0.4789
Vomiting	82 (5%)	65 (4%)	0.1525
Congestive heart failure	22 (1%)	15 (<1%)	0.2531
CHF in association with an absolute decrease of LVEF >15% from baseline and below LNL	6 (<1%)	3 (<1%)	0.3430
CHF in association with an absolute decrease of 15% ≥LVEF >10% from baseline and below LNL	1 (<1%)	1 (<1%)	1.0000
CHF with signs/symptoms from a clinical standpoint, regardless of LVEF decline	15 (<1%)	11 (<1%)	0.4402

AC → T, doxorubicin and cyclophosphamide followed by docetaxel; TAC, docetaxel, doxorubicin, and cyclophosphamide; ANC, absolute neutrophil count.

[a]Adverse events with an incidence of 1% or more in at least one treatment group are shown, as well as important long-term toxicities.

[b]Fisher's test P-value.

[c]ANC <1.0×10^9/l and fever ≥38.5°C.

'third-generation' regimens involving at least six cycles of taxane, anthracycline, and cyclophosphamide chemotherapy have been completed that share identical treatment arms. Most notably, the NSABP B38 study directly evaluated the relative merits of TAC and dose-dense every-2-week AC × 4 → paclitaxel (175 mg/m^2) × 4, and found no significant differences in efficacy [9]. However, toxicity profiles differed with higher rates of febrile neutropenia and diarrhea with TAC, and higher rates of neuropathy, anemia, transfusion, and erythropoietin use with dose dense AC → paclitaxel. Twelve-year follow-up of the ECOG-1199 study demonstrated that compared with the AC every-3-week paclitaxel arm, after a median follow-up of 12.1 years, DFS significantly improved for the weekly paclitaxel (HR, 0.84; $P = 0.011$) and the AC → T arm (HR, 0.79; $P = 0.001$), but no regimen significantly improved overall survival [5]. Taken together, these studies suggest equivalent efficacy among TAC, AC → T, every-2-week AC × 4 → paclitaxel (175 mg/m^2) × 4, and AC × 4 every 3 weeks followed by weekly paclitaxel for 12 doses. Consequently, the choice of regimen requires balancing differences in toxicity and treatment duration. TAC requires meaningfully fewer treatment visits (6), compared with 8 cycle regimens or the 16 treatment visits required for the AC → weekly paclitaxel, with attendant reduced times for chemotherapy infusion, nursing care, and patient travel. When used with primary prophylactic G-CSF to reduce hematologic complications, the TAC regimen provides a favorable global safety profile and allows a short duration of treatment, and remains an appropriate standard adjuvant regimen for women with operable HER2-negative breast cancer.

The BCIRG-005 study provides one of the longest follow-up analyses of a central laboratory defined and uniformly treated a large cohort of patients with a triple negative breast cancer. When the 604 patients with triple negative disease are compared with the hormone receptor-positive population, triple negative disease is a persistent and major poor prognostic feature (Figure 1C and D). Despite our earlier report that suggested these curves were approaching after a median follow-up of 5 years, the more mature 10-year data show a persistent and relatively uniform rate of relapse in both luminal and triple negative breast cancer populations (Figure 1C). The molecularly heterogeneity of both luminal and TNBC have been better defined in recent studies [10, 11], and while these curves undoubtedly represent the aggregate effect

of treatment-sensitive and -insensitive populations, further work is required to better define the chemotherapy-sensitive subgroups in node-positive breast cancer.

long-term toxicities

Two of the key life-threatening and life-changing long-term toxicities of adjuvant chemotherapy are secondary hematologic malignancies and cardiac dysfunction. In our study, rates of hematologic malignancy were within the range anticipated from other studies: 13 patients developed a hematologic malignancy (0.4%) and 6 patients (0.2%) died from leukemia or myelodysplastic syndrome.

Rates of congestive heart failure were relatively low (Table 2) with only 22 patients (1.3%) in the AC → T arm reported to develop any grade of CHF, and 15 (0.9%) in the TAC arm. There were no heart failure-related deaths reported despite 10 years of follow-up of a cohort of nearly 4000 anthracycline-treated patients. These results are in stark contrast to those reported in the 10-year follow-up of the BCIRG-001 study, in which 3.5% of 749 TAC-treated patients developed grade 3 or 4 CHF and 17% had significant decrease in LVEF [6]. The two studies have virtually identical baseline risks, anthracycline dosages were comparable in the regimens administered (300 mg/m^2 cumulative dose in TAC receiving patients and 240 mg/m^2 in the AC → T receiving patients), the duration of follow-up was 10 years in all studies, the majority of patients in the three studies came from the same centers, and survival outcomes [6, 7, 12] were similar. The critical distinction appears to be the intensity of follow-up for cardiac events. The BCIRG-005 population had no protocol-specified post-baseline cardiac evaluation; rather, investigators were instructed to follow the standard practice to investigate patients with symptoms suggesting cardiac dysfunction. In contrast, the BCIRG-001 study mandated regular LVEF determinations in long-term follow-up and presumably, due to this more intensive cardiac evaluation, found a higher percentage of patients with both symptomatic and asymptomatic cardiac toxicity. The lower rate of cardiotoxicity (both clinical and subclinical) in BCIRG-005 suggests the possibility of systemic underreporting and mis-identification of cardiac complications of adjuvant chemotherapy and are similar to those reported in most other adjuvant anthracycline studies. As summarized in the 2005 EBCCTG meta-analysis, anthracycline regimens resulted in a non-significant increase in annual risk of death from heart disease of 0.08% versus 0.06% per year in those receiving cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) [13]. Consequently, the 10-year rate of CHF found in BCIRG-005 is very similar to the 0.8% that would have been anticipated from the EBCCTG meta-analysis, in which the majority of contributing trials had no systematic cardiac follow-up. Symptoms of fatigue and decreased exercise tolerance are very frequent in women after completion of chemotherapy and may not trigger cardiac evaluation. In clinical practice, at least half of the heart failure-related deaths are due to arrhythmia, and it is possible that a proportion of the deaths from unknown cause without disease relapse in BCIRG-005 were related to cardiotoxicity. Given the clinical and subclinical cardiac issues that are a predictable consequence of standard doses of anthracycline therapy, formal studies evaluating strategies to reduce cardiac toxicities are warranted.

This 10-year analysis of the BCIRG-005 trial confirmed the efficacy of TAC was not superior to AC → T in women with node-positive early breast cancer, and we identified no subgroup where outcomes favored one regimen. The acute toxicity profiles differed between arms and were consistent with previous reports. The TAC regimen, when used with G-CSF as per current guidelines, provides shorter adjuvant treatment duration with fewer clinic visits and less acute toxicity. Long-term toxicities of leukemia and cardiotoxicity were similar between the two regimens. Patients with triple negative breast cancer, as determined by central FISH testing for the HER2 status and immunohistochemical assessment of receptor status, demonstrated a persistent risk of recurrence without evidence of a plateau or convergence with the outcomes of the hormone receptor-positive population. We conclude that TAC and AC → T are both acceptable chemotherapy regimens for the adjuvant therapy of node-positive breast cancer.

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disclosure

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Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial

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Background: In the PALOMA-3 study, palbociclib plus fulvestrant demonstrated improved progression-free survival compared with fulvestrant plus placebo in hormone receptor-positive, HER2– endocrine-resistant metastatic breast cancer (MBC). This analysis compared patient-reported outcomes (PROs) between the two treatment groups.

Patients and methods: Patients were randomized 2 : 1 to receive palbociclib 125 mg/day orally for 3 weeks followed by 1 week off ($n = 347$) plus fulvestrant (500 mg i.m. per standard of care) or placebo plus fulvestrant ($n = 174$). PROs were assessed on day 1 of cycles 1–4 and of every other subsequent cycle starting with cycle 6 using the EORTC QLQ-C30 and its breast cancer module, QLQ-BR23. High scores (range 0–100) could indicate better functioning/quality of life (QoL) or worse symptom severity. Repeated-measures mixed-effect analyses were carried out to compare on-treatment overall scores and changes from baseline between treatment groups while controlling for baseline. Between-group comparisons of time to deterioration in global QoL and pain were made using an unstratified log-rank test and Cox proportional hazards model.

Results: Questionnaire completion rates were high at baseline and during treatment (from baseline to cycle 14, ≥95.8% in each group completed ≥1 question on the EORTC QLQ-C30). On treatment, estimated overall global QoL scores significantly favored the palbociclib plus fulvestrant group [66.1, 95% confidence interval (CI) 64.5–67.7 versus 63.0, 95% CI 60.6–65.3; $P = 0.0313$]. Significantly greater improvement from baseline in pain was also observed in this group (–3.3, 95% CI –5.1 to –1.5 versus 2.0, 95% CI –0.6 to 4.6; $P = 0.0011$). No significant differences were observed for other QLQ-BR23 functioning

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