

Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial



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Summary

Background Tamoxifen is standard adjuvant treatment for postmenopausal women with hormone-receptor-positive breast cancer. We assessed the benefit of adding chemotherapy to adjuvant tamoxifen and whether tamoxifen should be given concurrently or after chemotherapy.

Methods We undertook a phase 3, parallel, randomised trial (SWOG-8814, INT-0100) in postmenopausal women with hormone-receptor-positive, node-positive breast cancer to test two major objectives: whether the primary outcome, disease-free survival, was longer with cyclophosphamide, doxorubicin, and fluorouracil (CAF) given every 4 weeks for six cycles plus 5 years of daily tamoxifen than with tamoxifen alone; and whether disease-free survival was longer with CAF followed by tamoxifen (CAF-T) than with CAF plus concurrent tamoxifen (CAFT). Overall survival and toxicity were predefined, important secondary outcomes for each objective. Patients in this open-label trial were randomly assigned by a computer algorithm in a 2:3:3 ratio (tamoxifen:CAF-T:CAFT) and analysis was by intention to treat of eligible patients. Groups were compared by stratified log-rank tests, followed by Cox regression analyses adjusted for significant prognostic factors. This trial is registered with ClinicalTrials.gov, number NCT00929591.

Findings Of 1558 randomised women, 1477 (95%) were eligible for inclusion in the analysis. After a maximum of 13 years of follow-up (median 8·94 years), 637 women had a disease-free survival event (tamoxifen, 179 events in 361 patients; CAF-T, 216 events in 566 patients; CAFT, 242 events in 550 patients). For the first objective, therapy with the CAF plus tamoxifen groups combined (CAFT or CAF-T) was superior to tamoxifen alone for the primary endpoint of disease-free survival (adjusted Cox regression hazard ratio [HR] 0·76, 95% CI 0·64–0·91; $p=0\cdot002$) but only marginally for the secondary endpoint of overall survival (HR 0·83, 0·68–1·01; $p=0\cdot057$). For the second objective, the adjusted HRs favoured CAF-T over CAFT but did not reach significance for disease-free survival (HR 0·84, 0·70–1·01; $p=0\cdot061$) or overall survival (HR 0·90, 0·73–1·10; $p=0\cdot30$). Neutropenia, stomatitis, thromboembolism, congestive heart failure, and leukaemia were more frequent in the combined CAF plus tamoxifen groups than in the tamoxifen-alone group.

Interpretation Chemotherapy with CAF plus tamoxifen given sequentially is more effective adjuvant therapy for postmenopausal patients with endocrine-responsive, node-positive breast cancer than is tamoxifen alone. However, it might be possible to identify some subgroups that do not benefit from anthracycline-based chemotherapy despite positive nodes.

Funding National Cancer Institute (US National Institutes of Health).

Introduction

The most common presentation of breast cancer is an oestrogen-receptor-positive tumour in postmenopausal women, for whom tamoxifen is the gold standard against which other systemic adjuvant treatments are compared.^{1–4} The addition of chemotherapy to endocrine therapy is attractive in theory,⁵ but there is no consensus about such treatment in postmenopausal women with tamoxifen-responsive disease.^{3,4} Individual phase 3 trials that compared chemotherapy plus tamoxifen with tamoxifen alone did not show a significant survival benefit in older women.^{6–9} A recent meta-analysis of

all existing trials based on individual patient data showed that the addition of chemotherapy to tamoxifen is only marginally beneficial in older women, by contrast with major survival improvements in premenopausal populations.¹⁰

Most individual trials in postmenopausal women tested the addition of regimens based on cyclophosphamide, methotrexate, and fluorouracil (CMF) to tamoxifen,^{3,4,6–8,10} but in some breast cancer study populations, CMF might be inferior to anthracycline-based regimens.^{11–16} No clinical trials have shown, however, that anthracycline-based therapy adds to the

Lancet 2009; 374: 2055–63

Published Online
December 10, 2009
DOI:10.1016/S0140-6736(09)61523-3

See Online/Comment
DOI:10.1016/S0140-6736(09)62097-3

See *Lancet Oncol*
DOI:10.1016/S1470-2045(09)70314-6
DOI:10.1016/S1470-2045(09)70347-X

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benefit of tamoxifen in postmenopausal patients with oestrogen-receptor-positive disease. Moreover, interference with drug-induced cytotoxicity was shown in vitro when tamoxifen was added to cancer cell lines concurrently with chemotherapy,^{17–20} yet concurrent tamoxifen and CMF has been common practice in clinical trials.

Our two objectives were to establish whether chemotherapy, consisting of 6 months of cyclophosphamide, doxorubicin, and fluorouracil (CAF) plus 5 years of tamoxifen, was superior to tamoxifen alone; and to assess whether CAF followed by tamoxifen was better than CAF plus concurrent tamoxifen. The CAF regimen we used was the most dose-intense combination among the commonly used regimens when this trial was designed.¹¹ This report presents long-term outcomes for both objectives.

Methods

Trial design

Southwest Oncology Group (SWOG)-8814, INT-0100 was a phase 3, parallel, three-group, open-label, randomised controlled trial. The trial was approved by the National Cancer Institute's Central Institutional Review Board, which manages all cooperative group trials, and the local review board at each institution. All patients gave written informed consent in the presence of an independent witness after the trial was explained by the treating oncologist. Progress of the trial and adverse event rates were reviewed by an independent data and safety monitoring committee every 6 months.

Participants

Postmenopausal women (defined in the protocol by use of standard National Cancer Institute criteria across all intergroup trials) with pathological stage T1–3, N1–2 (1988 criteria;²¹ excluding clinical N2) infiltrating adenocarcinoma of the breast were eligible for enrolment. Tumours were oestrogen-receptor positive or progesterone-receptor positive, or both, by biochemical assay

(≥ 10 fmol/mg) or classified as positive by immunohistochemistry according to institutional standards, with all tests done locally. Liver enzymes, chest radiograph, contralateral mammogram, and bone scan had to show no evidence of cancer. Definitive local therapy was modified radical mastectomy or lumpectomy with microscopically negative margins and axillary dissection. Radiotherapy was mandatory if a lumpectomy was done and optional after mastectomy if the stage was T3, four or more positive nodes were present, or if there was extranodal extension. Left-ventricular ejection fraction had to be normal, if done. Adequate renal, hepatic, and bone marrow function were required.

Randomisation and masking

Patients were randomly assigned in a 2:3:3 ratio to receive tamoxifen alone, CAF followed by tamoxifen (CAF-T), or CAF with concurrent tamoxifen (CAFT). Eligible patients were stratified by number of involved nodes (1–3 vs ≥ 4), progesterone-receptor status (positive vs negative), and interval from surgery (≤ 6 weeks vs > 6 weeks). Patients were allocated to treatment by a central software program that randomised within the cross-classification of the three stratifying variables with allocation probability to each treatment being determined by the sample size goals. After a centre had entered a patient's stratification variables, the computer generated, reported, and recorded the randomised assignment and patient identification number. It was not possible to know the next assignment since it was generated in real-time at the next registration. Blocking was not used. Both patient and treating physician were unmasked to randomisation assignment in this open-label study.

Interventions

CAF was given every 4 weeks for six cycles: cyclophosphamide 100 mg/m² orally on days 1–14; doxorubicin 30 mg/m² and fluorouracil 500 mg/m², both intravenously on days 1 and 8. The tamoxifen dose was 20 mg orally daily for 5 years. Dose reduction and toxicity reporting criteria were specified in the protocol. Standardised radiation treatment prescriptions were stipulated in the protocol. The radiation had to be completed before CAF or initiated after completion of CAF at the discretion of the physician. Radiation was begun on day 1 in the tamoxifen group. Patients were followed every 4 months for 5 years, every 6 months for 3 years, then yearly thereafter, even if patients withdrew early from treatment. Follow-up for late recurrence was terminated because of financial constraints, but mortality information is still obtained where possible.

Primary and secondary endpoints

The primary endpoint was disease-free survival, defined as the time from registration (randomisation) to breast cancer relapse (local or distant), new primary breast cancer, or death due to any cause, whichever came first.

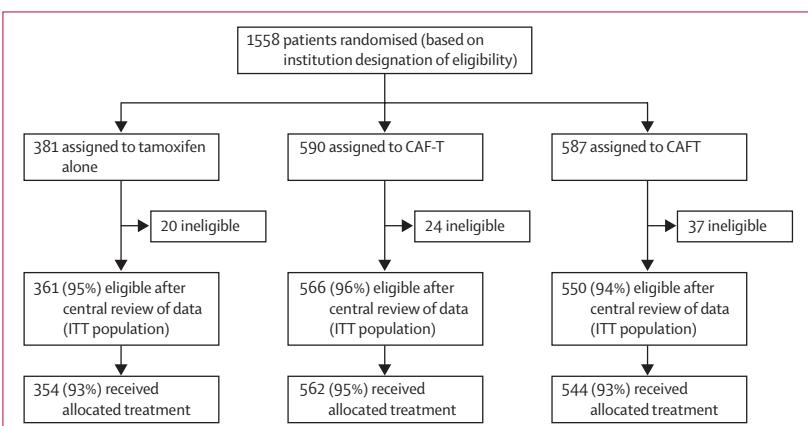


Figure 1: Trial profile

CAF-T=cyclophosphamide, doxorubicin, and fluorouracil (CAF) followed by tamoxifen. CAFT=CAF plus concurrent tamoxifen. ITT=intention-to-treat.

Patients who did not have an event were censored at the last follow-up visit. Prespecified secondary outcomes included overall survival and adverse event rates. Overall survival was defined as the time from registration until death due to any cause. Adverse events were graded according to the SWOG Toxicity Criteria included in the protocol.

Statistical analysis

The target sample size for each CAF plus tamoxifen group (530 patients per group) gave 89% power to detect a 33% increase in the hazard ratio (HR) for disease-free survival for CAFT versus CAF-T. The target sample size for the tamoxifen-alone group (350 patients) gave 90% power to detect a 25% reduction in the HR for disease-free survival for the combined CAF plus tamoxifen groups compared with tamoxifen alone. Although the protocol specified one-sided tests (with overall $\alpha=0.05$), only two-sided p values are reported here. The first interim analysis was to take place when the accrual was 75% complete ($\alpha=0.010$); the second was scheduled for 18 months after completion ($\alpha=0.013$). The final analysis was planned at $\alpha=0.04$ so that the combined level was $\alpha=0.05$ over all analyses.²²

The intention-to-treat analyses included all eligible patients, irrespective of the actual treatment subsequently received. Documentation of eligibility was assessed within a few months of randomisation and centrally reviewed before outcome information was available. Patients who did not meet eligibility criteria after final review were excluded from the analysis. Two planned analyses compared tamoxifen alone with the combined CAF plus tamoxifen groups (CAF-T plus CAFT), and CAF-T with CAFT. Secondary analyses that compared all three groups were added when interim results disclosed effect of tamoxifen timing on benefit from chemotherapy. We used Kaplan-Meier methods for estimation of survival times and stratified log-rank tests to test treatment effects using the three stratifying variables from randomisation.²³ Cox models were used to estimate HRs of treatment benefit adjusted for significant prognostic factors. All analyses were done with Stata version 10. This trial is registered with ClinicalTrials.gov, number NCT00929591.

Role of the funding source

The sponsor had no role in data analysis, writing of the report, or the decision to submit for publication. SWOG was responsible for data gathering and analysis. The corresponding author with SWOG had responsibility for the decision to submit for publication.

Results

Patients were enrolled from June, 1989, to July, 1995. Criteria for early stopping were not met at the first planned interim analysis. At the second interim analysis (after reaching the accrual goal), the comparison of

	Tamoxifen (n=361)	CAF-T (n=566)	CAFT (n=550)	All patients (n=1477)
Age (years)	60.0 (37–79)	60.7 (42–81)	61.8 (33–89)	61.3 (33–89)
≥65	117 (32%)	162 (29%)	191 (35%)	470 (32%)
>70	46 (13%)	62 (11%)	82 (15%)	190 (13%)
Ethnic origin				
White	307 (85%)	492 (87%)	453 (82%)	1252 (85%)
Black	38 (11%)	44 (8%)	57 (10%)	139 (9%)
Hispanic	11 (3%)	16 (3%)	23 (4%)	50 (3%)
Other	5 (1%)	14 (2%)	17 (3%)	36 (2%)
Number of involved axillary nodes				
1–3 positive	207 (57%)	334 (59%)	311 (57%)	852 (58%)
≥4 positive	154 (43%)	232 (41%)	239 (43%)	625 (42%)
Receptor status of tumour				
PgR-positive/ER-positive	261 (72%)	416 (73%)	414 (75%)	1091 (74%)
PgR-negative/ER-positive	84 (23%)	125 (22%)	111 (20%)	320 (22%)
PgR-positive/ER-negative	16 (4%)	25 (4%)	25 (5%)	66 (4%)
Tumour size T3	27 (7%)	40 (7%)	38 (7%)	105 (7%)
Type of primary therapy				
Breast conservation	69 (19%)	101 (18%)	109 (20%)	279 (19%)
Mastectomy	292 (81%)	465 (82%)	441 (80%)	1198 (81%)
Interval from definitive surgery				
≤6 weeks	257 (71%)	409 (72%)	378 (69%)	1044 (71%)
>6 weeks	104 (29%)	157 (28%)	172 (31%)	433 (29%)
Previous postmenopausal oestrogens				
Yes	76 (21%)	136 (24%)	121 (22%)	333 (23%)
No	285 (79%)	430 (76%)	429 (78%)	1144 (77%)

Data are n (%) or median (range). Percentages are based on the total in each treatment group. CAF-T=cyclophosphamide, doxorubicin, and fluorouracil (CAF) followed by tamoxifen. CAFT=CAF plus concurrent tamoxifen. ER=oestrogen receptor. PgR=progesterone receptor.

Table 1: Patient and tumour characteristics

tamoxifen alone with the combined CAF plus tamoxifen groups met criteria for reporting the primary outcome.²⁴ Additional follow-up was required for overall survival²⁵ and the first comparison of the two CAF plus tamoxifen groups.²⁶ Definitive 10-year estimates of disease-free survival and overall survival for both major objectives are now available. The early analyses reported HRs as tamoxifen alone versus CAF plus tamoxifen,^{24–26} whereas in this analysis they are reported as CAF plus tamoxifen versus tamoxifen alone to be consistent with current clinical trial publications.

The study population consisted of 1558 randomised women, of whom 1477 (95%) were eligible, with 361 assigned to tamoxifen; 566 to CAF-T; and 550 to CAFT (figure 1). Reasons for ineligibility were wrong stage or incomplete staging. The ineligibility rate did not differ by treatment assignment ($p=0.22$). 1460 (94%) patients received allocated treatment (figure 1). Patient and tumour characteristics were well balanced across the treatment groups (table 1). Analysis of treatment delivery showed that 166 (15%) of 1116 patients did not complete six cycles of CAF because of toxicity (n=115 [10%]), disease progression or death (n=7 [1%]), or other reasons (n=44 [4%]). Completion of treatment did not differ between the two

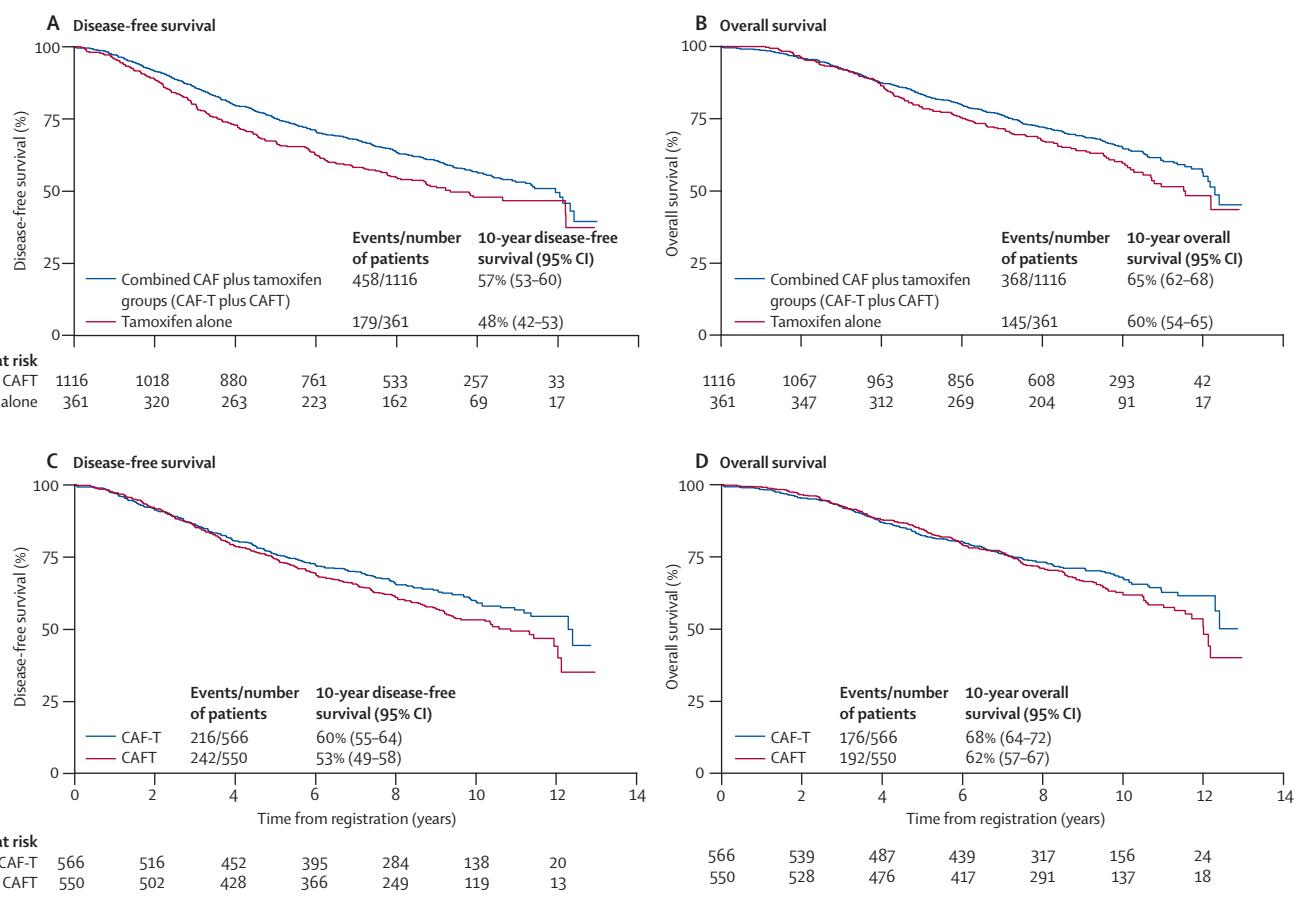


Figure 2: Disease-free survival and overall survival distributions and 10-year estimates for major objectives

Kaplan-Meier distributions for the intention-to-treat population. (A) Disease-free survival for the combined CAF plus tamoxifen groups (CAF-T plus CAFT) versus tamoxifen alone, log-rank $p=0.002$, stratified by number of positive nodes, hormone-receptor status, and time from definitive surgery. (B) Overall survival for the combined CAF plus tamoxifen groups versus tamoxifen alone, stratified log-rank $p=0.043$. (C) Disease-free survival for CAFT versus CAF-T, stratified log-rank $p=0.055$. (D) Overall survival for CAFT versus CAF-T, stratified log-rank $p=0.27$. CAF=cyclophosphamide, doxorubicin, and fluorouracil. CAF-T=CAF followed by tamoxifen. CAFT=CAF with concurrent tamoxifen.

CAF plus tamoxifen groups. Mean doses delivered (as percentage of planned doses) for cycles 1–3 were cyclophosphamide 86·6%, doxorubicin 86·1%, and fluorouracil 85·8%; for cycles 4–6 these proportions were 72·4%, 74·4%, and 71·8%, respectively. 81 (5%) of 1477 patients stopped tamoxifen early because of toxicity, 17 (1%) did not receive tamoxifen, and 112 (8%) discontinued tamoxifen early for reasons other than toxicity.

The first study objective, the comparison of tamoxifen alone with the combined CAF plus tamoxifen groups, was analysed for the primary disease-free survival and secondary overall survival endpoints. After a maximum of 13 years of follow-up (median 8·94 years), there were 179 (50%) events in 361 patients in the tamoxifen-alone group (149 relapses, nine new primary breast cancers, 21 deaths from causes other than breast cancer) and 458 (41%) events in 1116 patients in the combined CAF plus tamoxifen groups (318 relapses, 27 new primary breast cancers, 113 deaths from causes other than breast cancer). Disease-free survival was significantly longer in the combined CAF plus tamoxifen groups than in the

tamoxifen-alone group (stratified log-rank test $p=0.002$; figure 2A). 10-year disease-free survival estimates were 57% (95% CI 53–60) for the combined CAF plus tamoxifen groups and 48% (42–53) for the tamoxifen-alone group. Compared with the tamoxifen group, the HR for disease-free survival in the combined CAF plus tamoxifen groups was 0·76 (95% CI 0·64–0·91; $p=0.002$) by Cox regression, adjusted for the other significant independent prognostic factors of nodal status, receptor status, tumour size, and black ethnic origin (table 2).

Overall survival was significantly longer in the combined CAF plus tamoxifen groups than in the tamoxifen-alone group (stratified log-rank test $p=0.043$; figure 2B). The Kaplan-Meier survival curves began to diverge after the fourth year and remained separate for the rest of the study. 10-year overall survival estimates were 65% (62–68) for the combined CAF plus tamoxifen groups and 60% (54–65) for the tamoxifen-alone group. The adjusted HR for overall survival for the combined CAF plus tamoxifen groups compared with the tamoxifen-alone group was 0·83 (0·68–1·01; $p=0.057$; table 2).

Exploratory, unplanned analyses showed that benefit from the addition of CAF to tamoxifen for disease-free survival and overall survival was seen in most major subsets listed in table 1. The unadjusted HRs for disease-free survival for these subgroups suggest that there might be variation in the efficacy of chemotherapy, particularly with number of positive nodes and age (figure 3). Patients with four or more positive nodes derived more benefit than did those with one to three positive nodes (test for interaction $p=0.015$, adjusted for prognostic factors) and patients less than 65 years might have had a greater degree of benefit than did older patients (test for interaction $p=0.13$, adjusted for prognostic factors; table 2). Additional variation of the unadjusted HRs in figure 3 might be attributable to small numbers or factors associated with number of positive nodes, such as the type of surgical procedure used.

The second study objective—the comparison of CAF-T with CAFT—was analysed for the primary disease-free survival and secondary overall survival endpoints. Event rates were lower than predicted and there was late separation of the CAF-T and CAFT survival curves for disease-free survival (figure 2C) and overall survival (figure 2D). Disease-free survival for CAF-T was marginally superior to CAFT (stratified log-rank test, $p=0.055$), with 10-year estimates of 60% and 53%, respectively. The adjusted HR for disease-free survival (table 2) was 0.84 (0.70–1.01; $p=0.061$) for CAF-T compared with CAFT. The difference in overall survival was not significant (stratified log-rank test, $p=0.27$), with 10-year estimates of 68% and 62%, respectively, and adjusted HR (table 2) of 0.90 (0.73–1.08; $p=0.30$) for CAF-T compared with CAFT.

Secondary three-way comparisons were undertaken for the primary and secondary endpoints, because the timing of tamoxifen treatment affected the degree of benefit from CAF. The three-sample stratified log-rank tests were significant for disease-free survival (figure 4A; $p=0.002$), but did not quite reach significance for overall survival (figure 4B; $p=0.074$). The adjusted HR for disease-free survival for CAF-T was 0.70 (0.57–0.85; $p=0.0002$) and the HR for CAFT was 0.83 (0.69–1.01; $p=0.062$) compared with tamoxifen alone (table 2). For overall survival, the adjusted HRs were 0.79 (0.63–0.98; $p=0.032$) and 0.87 (0.70–1.08; $p=0.22$) for CAF-T and CAFT, respectively, compared with tamoxifen alone. The absolute 10-year benefits in disease-free survival for CAF-T and CAFT over tamoxifen were 12% and 5%, respectively (figure 4A).

513 women died during the study (tamoxifen, n=145; CAF plus tamoxifen, n=368). Deaths from causes other than acute treatment toxicity or breast cancer occurred in 147 (10%) patients (29% of deaths). 73 (22%) of 337 deaths in women aged less than 65 years at study entry were not caused by breast cancer or acute toxicity compared with 74 (42%) of 176 deaths in women aged 65 years or older. Specific ascertainment of the reason

for these deaths (competing or unrelated cause vs late toxicity) was not possible.

Mortality and morbidity during year 1 of treatment for the tamoxifen alone and combined CAF plus tamoxifen groups are shown in table 3. Events were more frequent in patients assigned to CAF than in those assigned to

	Disease-free survival		Overall survival	
	HR (95% CI)	Two-sided p value	HR (95% CI)	Two-sided p value
Primary comparisons				
Combined CAF plus tamoxifen groups vs tamoxifen alone	0.76 (0.64–0.91)	0.002	0.83 (0.68–1.01)	0.057
CAF-T vs CAFT	0.84 (0.70–1.01)	0.061	0.90 (0.73–1.10)	0.30
Secondary comparisons				
CAF-T vs tamoxifen alone	0.70 (0.57–0.85)	0.0002	0.79 (0.63–0.98)	0.032
CAFT vs tamoxifen alone	0.83 (0.69–1.01)	0.062	0.87 (0.70–1.08)	0.22
Relevant subset comparisons for combined CAF plus tamoxifen groups vs tamoxifen alone				
Number of involved axillary nodes†				
1–3 positive nodes	0.98 (0.75–1.29)	0.91	0.95 (0.70–1.29)	0.76
≥4 positive nodes	0.63 (0.50–0.79)	<0.0001	0.75 (0.59–0.97)	0.026
Age (years)‡				
<65	0.70 (0.57–0.86)	0.001	0.79 (0.62–1.00)	0.049
≥65	0.94 (0.69–1.29)	0.72	0.95 (0.68–1.33)	0.76
CAF=cyclophosphamide, doxorubicin, and fluorouracil. CAF-T=CAF followed by tamoxifen. CAFT=CAF plus concurrent tamoxifen. *Black ethnic origin, nodal status, receptor status, tumour size. †Test for interaction $p=0.015$ for disease-free survival; $p=0.26$ for overall survival. ‡Test for interaction $p=0.13$ for disease-free survival; $p=0.44$ for overall survival.				

Table 2: Survival outcomes by treatment adjusted for significant factors in the Cox multivariate model*

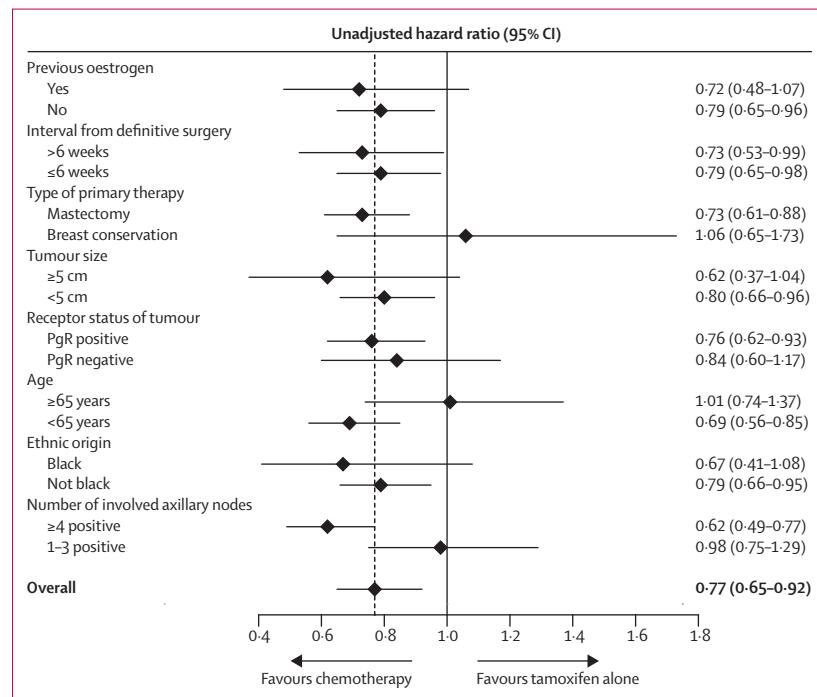


Figure 3: Hazard ratios and 95% CIs for disease-free survival, by subgroup

The forest plot shows the disease-free survival advantage for chemotherapy by possible subgroups unadjusted for other covariates. The dashed vertical line represents the overall unadjusted hazard ratio in each plot. PgR=progesterone.

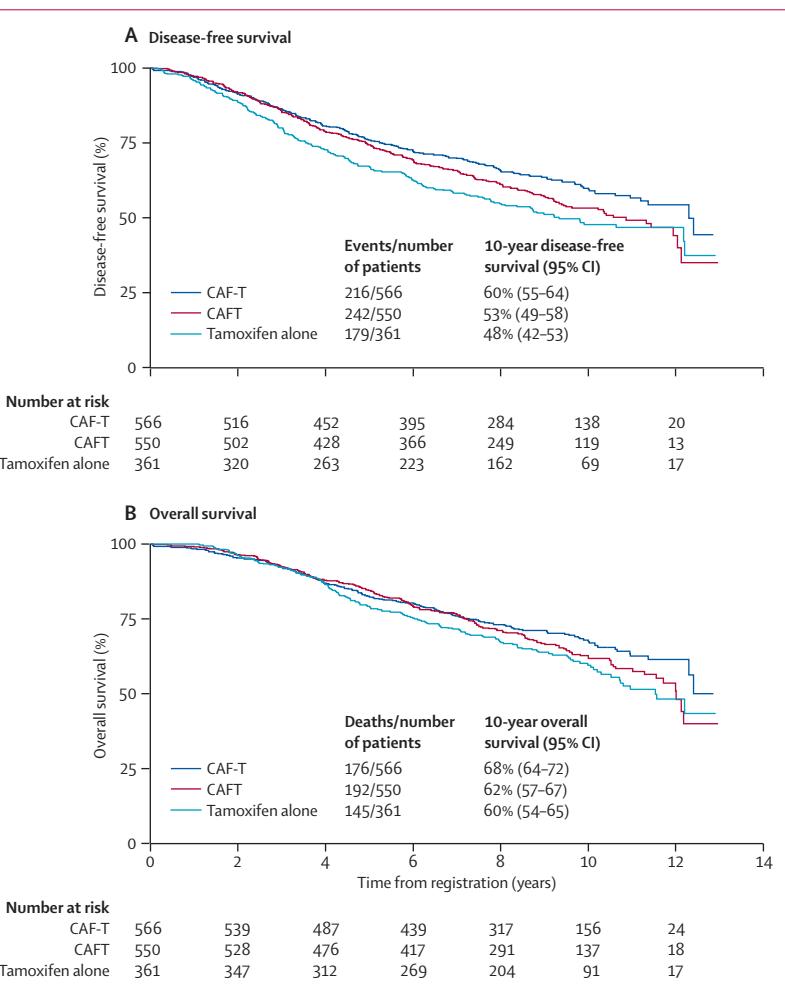


Figure 4: Disease-free survival and overall survival by randomised treatment group

Kaplan-Meier distributions for the intention-to-treat population. (A) Disease-free survival advantage for CAF-T, log-rank p=0.002, stratified by number of positive nodes, hormone-receptor status, and time of surgery. (B) Superior overall survival in the CAF-T group, stratified log-rank p=0.074. 10-year survival estimates and hazard ratios adjusted for prognostic covariates with 95% CIs are also shown. CAF-T=cyclophosphamide, doxorubicin, and fluorouracil (CAF) followed by tamoxifen. CAFT=CAF plus concurrent tamoxifen.

tamoxifen alone. In the combined CAF plus tamoxifen groups there were four deaths during CAF and the incidence of grade 4 neutropenia was 44%, but neutropenic fever was uncommon. Grade 2–4 emesis or stomatitis was seen in 255 (23%) and 294 (27%) patients, respectively. There were 40 (3.6%) thrombotic events during CAF (mainly deep vein thromboses), ten (0.9%) reports of grade 3–4 congestive heart failure, and four patients had grade 1–2 decline of ejection fraction. No differences in toxicity were noted between treatment with CAF-T and CAFT.

Table 3 also shows late treatment-related adverse events in 1430 patients who completed 1 year without early relapse. Congestive heart failure was reported in 25 patients (0.36 per 100 person-years) in the combined CAF plus tamoxifen groups and in one patient (0.048 per 100 person-years) in the tamoxifen-alone group. Pulmonary

	Tamoxifen	Combined CAF plus tamoxifen groups (CAF-T plus CAFT)*
Early events (first year of treatment; %)†		
Death	0	4 (0.36%)
Grade 4 neutropenia	0	491 (44.4%)
≥Grade 2 emesis	1 (0.28%)	255 (23.1%)
≥Grade 2 stomatitis/mucositis	2 (0.56%)	294 (26.6%)
Thromboembolic episodes	0	40 (3.6%)
Cardiac events		
Grade 1–2 ejection fraction decline	0	4 (0.36%)
Grade 3–4 congestive heart failure	0	10 (0.90%)
Late events (after year 1, no relapse; rate‡)§		
Congestive heart failure¶	1 (0.048)	25 (0.36)
Any grade thromboembolic event	7 (0.33)	24 (0.34)
Uterine neoplasm	4** (0.16)	15†† (0.19)
Endometrial	3 (0.12)	14 (0.17)
Sarcoma	1 (0.041)	1 (0.012)
AML/MDS	0	9 (0.14)

CAF=cyclophosphamide, doxorubicin, and fluorouracil. CAF-T=CAF followed by tamoxifen. CAFT=CAF plus concurrent tamoxifen. AML=acute myeloid leukaemia. MDS=myelodysplastic syndrome. *No significant difference in any event between the CAF plus tamoxifen groups (CAFT, CAF-T). †Tamoxifen, n=354; CAF plus tamoxifen groups, n=1106. ‡Rate per 100 person-years of follow-up to relapse or last contact. §Tamoxifen, n=346; CAF plus tamoxifen groups, n=1084. ¶Excludes heart failure resulting from coronary artery disease. ||Includes one death from pulmonary embolism at year 1. **Includes one death from uterine sarcoma. ††Includes two deaths (one uterine sarcoma; one endometrial carcinoma).

Table 3: Mortality and morbidity during the first and subsequent years of treatment

embolism, deep venous thrombosis, or stroke occurred in 24 patients (0.34 per 100 person-years) assigned to CAF plus tamoxifen and in seven patients (0.33 per 100 person-years) assigned to tamoxifen alone. The rates of non-breast second primary malignancies in the tamoxifen-alone group were similar to those in the CAF plus tamoxifen groups, apart from secondary acute myeloid leukaemia or myelodysplastic syndrome (tamoxifen, no events; CAF-T plus CAFT, nine events [0.14 per 100 person-years]). There were 19 uterine malignancies, (tamoxifen, 0.16 per 100 person-years; CAF-T plus CAFT, 0.19 per 100 person-years). Rates for all of these adverse events were similar in the CAFT and CAF-T groups (data not shown).

Discussion

We found that adjuvant treatment with a combination of CAF plus tamoxifen significantly improved disease-free survival compared with tamoxifen alone in postmenopausal women with node-positive, hormone-receptor-positive breast cancer. This advantage was greater in women with four or more positive nodes and in younger postmenopausal women (aged <65 years), although benefit cannot be ruled out for women with one to three positive nodes or for older women. A separate report describes subgroups of patients from this study (based on multigene analyses of tumours)

who do not seem to benefit, despite the overall trial finding that CAF plus tamoxifen is beneficial compared with tamoxifen alone.²⁷

The other primary objective of this study was to investigate whether potential antagonism between tamoxifen and chemotherapy (suggested by preclinical data^{17–20}) was manifested by a worse clinical outcome for concomitant therapy than with sequential treatment. The magnitude of benefit for disease-free survival when CAF was added to tamoxifen seemed greater when this drug followed chemotherapy than when it was given concurrently. Two small trials prospectively addressed timing of tamoxifen administration in relation to chemotherapy, but neither reported a significant difference in outcome between concurrent and sequential treatment.^{28,29} There are several reasons why concurrent tamoxifen could interfere with chemotherapy,^{17–20} but none of them has been conclusively proven.

Overall survival was an important secondary outcome in this population of postmenopausal women. Whereas overall survival showed the same general trend as disease-free survival, the HRs were attenuated and significance was not reached. This study supports the use of disease-free survival as a primary outcome because of reduced follow-up time, but also shows that reaching significance for overall survival might require longer follow-up in patients with endocrine-responsive breast cancer.

Our data support the use of anthracycline-based chemotherapy followed by tamoxifen in clinical practice. On the basis of our results, the recent St Gallen consensus recommended that tamoxifen should be started after chemotherapy,⁴ and this approach is current policy for major cooperative group adjuvant studies. However, the concerns about concomitant tamoxifen with chemotherapy that were raised by this study should not be extrapolated to aromatase inhibitors, the other major form of endocrine adjuvant therapy, since they work by a different mechanism in the cell. The optimum timing of these agents with respect to chemotherapy has not been studied.

It is common practice to omit chemotherapy from the systemic therapy adjuvant prescription in postmenopausal women. This practice standard, recommended for some nodal and oestrogen-receptor expression level subgroups in the St Gallen consensus, is based on the small benefit of chemotherapy reported in a meta-analysis¹⁰ and in individual trials that showed no added benefit of chemotherapy.^{7–9} Most of these studies were CMF-based, prescribed tamoxifen concurrently with chemotherapy, used intravenous cyclophosphamide in the CMF regimen, or prospectively lowered doses of chemotherapy in relation to increasing patient age.

Instead, our results suggest that anthracycline-based approaches for approximately 6 months could help to achieve maximum benefit from chemoendocrine therapy in postmenopausal women with hormone-receptor-

positive breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) reported a disease-free survival advantage from four cycles of doxorubicin plus cyclophosphamide added to tamoxifen over tamoxifen alone, but overall survival in the two groups was not significantly different ($p=0.08$), although premenopausal patients and those with receptor-negative disease were also included in the study.³⁰ Another group reported an advantage in disease-free survival but not in overall survival of six cycles of fluorouracil, epirubicin, and cyclophosphamide in postmenopausal women with oestrogen-receptor-positive breast cancer and one to three positive nodes.³¹

There are several limitations to our study. First, we do not know which women would benefit from added chemotherapy compared with endocrine therapy alone. A subset of women with oestrogen-receptor-positive breast cancer have endocrine-responsive tumours (defined by very high levels of receptor expression) that show different biology and might not be as responsive to chemotherapy.^{4,9} The benefit of CAF seen in our study might not occur in all patient subsets. A separate report addresses this important question of chemotherapy benefit within biological subsets.²⁷ Second, this study was done in the era before standard determination of HER2 (ERBB2) status of the breast tumour; therefore, some of the chemotherapy benefit might have occurred in the HER2-positive subgroup within this trial population. This important issue is also considered in the separate report.²⁷ Third, the small sample size (by current standards) limits the power to make definitive conclusions in key subgroups. Finally, there was no central determination of oestrogen-receptor status to confirm the institutional designation of positive. This aspect was addressed in the separate report.²⁷

The disease-free survival advantage from CAF-based treatment was not without significant toxicity in some women, such that the frequent as well as more infrequent toxicities and late events seen should be fully presented at time of the treatment decision-making process. There was an increased risk of thrombotic episodes during the first year of chemoendocrine therapy, as reported by others,⁸ and no difference in the risk between CAF-T and CAFT. Congestive heart failure was uncommon, but occurred at a greater frequency in the combined CAF plus tamoxifen groups than in the tamoxifen-alone group; the anthracycline was probably responsible for this adverse event. The risk of late acute myeloid leukaemia or myelodysplastic syndrome was less than 1%, but the conditions were only seen in the combined CAF plus tamoxifen groups (no difference between CAFT and CAF-T) and not in the tamoxifen-alone group.

We believe that for postmenopausal women with few comorbidities who have a substantial risk of recurrence or death based on the prognostic profile of their tumour, the risk–benefit balance favours anthracycline-based chemotherapy followed by tamoxifen. However,

characteristics of the tumour should also be factored into the risk–benefit ratio. This study shows the necessity of long-term follow-up of adjuvant therapies to determine the outcomes of treatment.

Contributors

KSA was the principal investigator and participated in study design, writing the protocol, approval of the final draft of the protocol, patient accrual, study monitoring, data and toxicity review, discipline review, final data analyses, interpretation of results, writing of the report, and review of the completed report. HBM participated in approval of the final draft of the protocol, patient accrual, study monitoring, data and toxicity review, discipline review, and final data analyses. SJG participated in study design, writing the protocol, approval of the final draft of the protocol, study monitoring, data and toxicity review, and final data analyses. WEB, DL, RBL, SM, and CKO participated in final data analyses. KIP, ASL, ICH, MDA, and CKO participated in study design. JNI, KIP, ASL, MDA, and CKO participated in protocol writing or review and approval of the final protocol. PMR, EGL, KIP, DJS, and RBL participated in study monitoring, and toxicity and data review. WBF, GVB, SJK, CDC, EGL, JNI, KIP, ASL, SM, and CKO participated in patient accrual. ASL and DJS participated in discipline review. WEB, PMR, CDC, JNI, KIP, HBM, SJG, RBL, SM, and CKO participated in interpretation of results and in writing or reviewing the completed report. GVB, SJK, EGL, ASL, ICH, DJS, and WBF participated in writing of the report or review of the completed report. All authors have approved the final report for publication, with the exception of MDA who died after initial data interpretation and manuscript draft approval.

The Breast Cancer Intergroup of North America

Southwest Oncology Group (SWOG), Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), National Cancer Institute of Canada Clinical Trials Group (NCIC), North Central Cancer Treatment Group (NCCTG).

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This study was solely supported by the National Cancer Institute as a High Priority Trial and was undertaken by the Southwest Oncology Group (SWOG) for The Breast Cancer Intergroup of North America. The investigation was supported in part by the following PHS Cooperative Agreement grant numbers awarded by the National Cancer Institute, Department of Health and Human Services: CA38926, CA32102, CA21115, CA02599, CA60138, CA25224, CA77202-06, CA04920, CA58658, CA13612, CA37981, CA76447, CA22433, CA58416, CA20319, CA58686, CA04919, CA46441, CA58861, CA27057, CA32734, CA35281, CA12644, CA16385, CA45560, CA58882, CA14028, CA35176, CA46282, CA46113, CA52650, CA03096, CA28862, CA35090, CA58723, CA35283, CA45807, CA35200, CA35119, CA45450, CA46136, CA42777, CA35261, CA45466, CA35117, CA46368, CA58348, CA12213, CA52654, CA35128, CA58415, CA52623, CA35192, CA45377, CA35996, CA52757, CA76132, CA35431, CA76462, CA45461, CA35084, CA76429, CA35178, CA67663, CA63844, CA52772. We thank The Breast Cancer Intergroup of North America discipline leaders for their advice or assistance during the design or conduct of this study. We thank the membership of the Breast Committees of SWOG, ECOG, NCCTG, CALGB, and NCIC for their support of this study over the long accrual period. We also thank the survivors of breast cancer who were treated and followed-up on this protocol.

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