Polychemotherapy for Early Breast Cancer: Results From the International Adjuvant Breast Cancer Chemotherapy Randomized Trial

The Adjuvant Breast Cancer Trials Collaborative Group

Background Survival of patients with early-stage breast cancer is improved following treatment with single-modality tamoxifen, ovarian ablation or suppression, or chemotherapy. The Adjuvant Breast Cancer Trials were designed to ascertain any additional benefits of combined treatment.

Methods The Adjuvant Breast Cancer Chemotherapy Trial was a randomized phase III trial in which patients with early-stage breast cancer who were receiving prolonged (5 years) tamoxifen treatment, with or without ovarian ablation or suppression, were randomly assigned to standard chemotherapy versus none. Trial endpoints included relapse-free and overall survival. Hazard ratios (HRs) were derived from Cox models, and all statistical tests were two-sided.

Results Between 1992 and 2000, 1991 patients between the ages of 26 and 81 years were randomly assigned (987 to chemotherapy, 1004 to no chemotherapy) from 106 UK and 16 non-UK centers. Nine hundred seven (92%) patients received chemotherapy as allocated (87% received cyclophosphamide, methotrexate, and 5-fluorouracil; 11% received anthracycline-containing regimens). A total of 244 of the 619 premenopausal patients received elective ovarian ablation or suppression. Chemotherapy improved relapse-free survival (relapse in the chemotherapy group versus no-chemotherapy group, 298 events versus 332 events, HR = 0.86, 95% confidence interval [CI] = 0.73 to 1.01; $P = .06$) and overall survival (death from any cause in the chemotherapy group versus no-chemotherapy group, 243 events versus 282 events, HR = 0.83, 95% CI = 0.70 to 0.99; $P = .03$) after adjustment for nodal status, estrogen receptor status, and age. Subgroup analyses showed that the benefit of chemotherapy was greatest in younger women (<50 years) and in particular for premenopausal women not receiving ovarian ablation or suppression.

Conclusion Modest yet sustainable benefits for chemoendocrine therapy occur in women with breast cancer. However, the full impact on overall survival may not emerge for several years.

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In 1992, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) systematic overview of randomized trials reported that prolonged tamoxifen treatment, chemotherapy, and ovarian ablation or suppression were similarly efficacious when given as single-modality treatments in pre- and perimenopausal women with early breast cancer (1). Historically, trials were too small individually to fully characterize the effectiveness of these agents. Nevertheless, a striking finding was the observed effects of prolonged (>2 years) tamoxifen treatment in young women (aged < 50 years)—a reduction of 43% in annual odds of relapse (or intercurrent death) and of 27% in annual odds of death from any cause (1)—identifying a benefit consistent with that already recognized for older women. This finding ushered in the era of prolonged tamoxifen (usually 5 years) as an alternative or adjunct to chemotherapy, given its simplicity of oral administration, relatively low morbidity (2), and low cost.

The lack of published data precluded the EBCTCG overview from reliably assessing the benefits of combined tamoxifen, chemotherapy, and ovarian ablation or suppression, or the degree of independence of their effects. Although the data suggested a reduction in risk of recurrence in women receiving both tamoxifen and chemotherapy, the duration of tamoxifen therapy was short (<2 years), and there were too few deaths to provide reliable evidence relating to overall survival. In addition, in trials testing

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chemotherapy plus or minus tamoxifen, the duration of tamoxifen therapy was, on average, only 1.6 years, whereas tamoxifen therapy duration in trials testing tamoxifen alone versus none was substantially longer (mean = 2.6 years).

With regard to postmenopausal women, among whom the benefits of adjuvant tamoxifen were already well established (3), the 1992 updated EBCTCG overview confirmed that the addition of chemotherapy to tamoxifen led to a statistically significant improvement in relapse-free survival. However, data on overall survival were limited, and it was not clear whether the benefits of chemotherapy were maintained against a background of prolonged tamoxifen treatment, given the relatively short duration of tamoxifen treatment prescribed in many trials.

In the early 1990s, a chemotherapy regimen consisting of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) (4) was the most commonly used regimen in patients with early breast cancer, with use of anthracyclines beginning to emerge for some women with a high risk of disease relapse. At that time, in the United Kingdom, testing for estrogen receptor (ER) status was not routinely available, and the EBCTCG overview had suggested a benefit for tamoxifen in both ER-positive (+) and ER-negative (–) breast cancer. Therefore, in late 1992, the Adjuvant Breast Cancer (ABC) Trials were initiated to further assess the benefits of combined modality therapy, including ovarian suppression or ablation in pre- and perimenopausal women against a background of 5 years of tamoxifen for all patients with early breast cancer. The trials were designed to focus on long-term outcomes, in particular, overall survival. The ABC Chemotherapy (CT) Trial tested the addition of chemotherapy to prolonged tamoxifen (with or without elective ovarian ablation or suppression) in the pre- and perimenopausal group, and the ABC Ovarian Ablation or Suppression (OAS) Trial assessed the addition of ovarian ablation or suppression to prolonged tamoxifen (with or without elective chemotherapy) in pre- and perimenopausal women only. The ABC Trials are now mature and provide the opportunity to describe long-term outcomes and to characterize any benefits according to clinical prognostic factors and age at diagnosis. Here we report the results of the ABC (CT) Trial.

CONTEXT AND CAVEATS

Prior knowledge

Single-modality treatment with tamoxifen, ovarian suppression or ablation, or chemotherapy improves the survival of women with early-stage breast cancer.

Study design

Randomized controlled phase III clinical trial of tamoxifen treatment in combination with chemotherapy and/or ovarian ablation or suppression.

Contributions

Women who had chemotherapy had improved relapse-free and overall survival compared with those who did not have chemotherapy. Improvements were seen especially among women younger than age 50 years and premenopausal women who did not receive ovarian ablation or suppression.

Implications

Chemotherapy combined with endocrine therapy (tamoxifen) may improve outcomes of women with early-stage breast cancer.

Limitations

Due to improvements in breast cancer treatment since the study began, current regimens and criteria for treatment are different from those used in the study. Thus, the benefits of current therapies may be greater than those observed in this study.

Methods

Design

The ABC (CT) Trial aimed to identify the added benefits of chemotherapy in addition to prolonged tamoxifen treatment among women with early-stage invasive breast cancer (and with or without elective ovarian ablation or suppression in pre- and perimenopausal women). All patients were scheduled to receive prolonged tamoxifen [5 years unless patient was entered into the Does Adjuvant Tamoxifen Treatment Offer More? (5) or Adjuvant Tamoxifen Longer Against Shorter (6) trials of tamoxifen duration] and were randomly assigned to either chemotherapy or no chemotherapy. In pre- and perimenopausal women, use of ovarian ablation or suppression was at the clinician's discretion (including the option for the patient to be entered into the ABC [OAS] Trial), but with a requirement to declare such treatment before random assignment into the ABC (CT) Trial. A total of 281 patients were entered into both the ABC (CT) and ABC (OAS) Trials.

The primary endpoint was overall survival, based on all-cause mortality. Secondary endpoints included relapse-free survival and breast cancer mortality (not reported here).

Eligibility

Eligible patients were women with histologically confirmed early-stage operable (T1-3a N0-1 M0) invasive breast cancer. Patients could have had no previous malignancy (except cervical cancer in situ or basal cell carcinoma) and no previous systemic therapy for their current breast cancer and had to be available for follow-up. The trial was open to recruitment from December 4, 1992, to October 2, 2000.

Evaluation of Estrogen Receptor Status

For patients who had unknown ER status at random assignment, retrospective testing of the ER was subsequently carried out centrally on the majority of tumor samples from women residing in the United Kingdom (and some non-UK). Testing was carried out by immunohistochemistry using paraffin-embedded tissue or obtained from local hospitals where information on ER status is now available.

To obtain ER status, at least two 5-μm-thick sections were cut from a representative paraffin block onto a SuperFrostPlus glass slide, dewaxed through xylene and alcohol changes, and antigen retrieved by heating in 10 mM EDTA solution, pH 8.0, at full power in an 800-W microwave oven. After blocking of the endogenous peroxidase, the section was treated sequentially at room temperature with a mouse monoclonal anti-ER antibody (1:40, 45 minutes, Novocastra, Newcastle, UK), secondary detection kit reagents (30 minutes each reagent, ChemMate S3006, DakoCytomation, Ely, Cambridge, UK), diaminobenzidine substrate solution

(10 minutes, DakoCytomation), and a lightly applied hemotoxylin nuclear counterstain. The immunostained slides were evaluated for the level of nuclear ER expression with <10% expression as a cut point for a negative result. The scores representative of 10%–25%, 25%–50%, 50%–75%, and 75%–100% tumor nuclear staining were interpreted as borderline, weak, moderate, and strong positive, respectively. The scoring system was adapted as a simplified version of the clinically validated Quick Score method (7,8).

Treatment

The chemotherapy regimen to be used was at the clinicians' discretion but was to be according to center policy and declared before random assignment. Recommended schedules were CMF (cyclophosphamide at a dose of 100 mg/m^2 orally days 1–14; methotrexate at 40 mg/m^2 intravenously (iv) days 1 and 8; 5-fluorouracil 600 mg/m^2 iv days 1 and 8 repeated at 28-day intervals for a total of six cycles) (3) or AC (doxorubicin at a dose of 60 mg/m^2 iv day 1; cyclophosphamide at 600 mg/m^2 iv day 1 repeated at 21-day intervals for a total of four cycles) (9). Recommended dose reductions were defined for hematologic and mucosal toxicity. Chemotherapy was to begin within 4 weeks of random assignment.

Surgery and radiotherapy were carried out according to local policy but within protocol-specified recommendations. Radiotherapy was allowed concurrently with chemotherapy or at the end of treatment. Tamoxifen (20 mg/day) was prescribed for a minimum of 5 years in all patients starting within 4 weeks of primary surgery and concurrently with chemotherapy, if given. Ovarian ablation or suppression was permitted (as described above) and scheduled according to local practice.

Ethics and Governance

A Patient Information Sheet was provided, and all patients gave consent, according to the requirements of the participating institution. Ethics committee approval was sought initially from each local research ethics committee and subsequently, once established, from a UK multicenter research ethics committee. The trial was conducted in accordance with the UK Medical Research Council's principles of Good Clinical Practice. This study is registered as an International Standard Randomized Controlled Trial, number ISRCTN31514446.

Trial Management

Randomization and data management were carried out at four academic trials units in the United Kingdom (The Institute of Cancer Research—Clinical Trials and Statistics Unit [ICR-CTSU], Sutton; Information and Statistics Division Cancer Clinical Trials Team, Edinburgh; Cancer Research UK Clinical Trials Unit, Birmingham; and the Clinical Trials Research Unit, University of Leeds, Leeds) and at the Ministry of Health Clinical Trials and Epidemiology Research Unit, Singapore. Data were collated annually at ICR-CTSU, where interim and final analyses were conducted.

Data Collection and Follow-up

Patients were followed up annually via their participating hospital. All UK patients were flagged through the Office for National Statistics. Case report forms included a minimum defined dataset required to assess the main endpoints and a summary assessment of treatment compliance. Analysis was based on follow-up received by the trials units to June 30, 2004. Annual follow-up continues for all patients who are available for follow-up.

Relapses were diagnosed according to local practice. Local relapse was defined as cancer recurrence in or on the ipsilateral chest wall/breast, and all other sites of relapse were classified as distant metastases.

No individual adverse event data were recorded because the toxicity profile of trial treatments was considered to be well characterized; however, patient-reported symptomatology was recorded in the subset of patients in an associated Quality of Life study. In response to a report in the literature of increased thromboembolic events with concomitant tamoxifen and chemotherapy (10), prospective recording of thromboembolic events up to 1 year postrandomization was introduced midtrial.

Quality of Life

The associated Quality of Life study was initiated in 1997 in 31 UK centers. All patients who entered the main trial from these centers were invited to participate in the Quality of Life study. Quality of Life assessments were obtained at baseline (prerandomization) at 3, 6, 9, 18, 30, 48, and 72 months. The self-completion surveys used included the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (11), EORTC BR23 (12), the Hospital Anxiety and Depression Scale (13), a Sexual Activity Questionnaire (14), and questions on menopausal symptoms and resource use EQ5D (15). The night sweats symptom scores used a four-point response scale, with the summary score calculated according to the EORTC manual (16).

Statistical Analysis

Treatment allocation was by random assignment, using randomly permuted blocks stratified by hospital, menopausal status, and elective ovarian ablation or suppression treatment and with a 1:1 treatment allocation ratio.

Five-year overall survival of women who received single-modality systemic therapy was anticipated to be approximately 75% (1). It was judged that the addition of chemotherapy to prolonged tamoxifen (with or without ovarian ablation or suppression in pre- and perimenopausal women) would be of clinical benefit if 5-year overall survival improved from 75% to 80%. Based on this assumption and using a two-sided log-rank test ($\alpha = 0.05$), 492 events were required for 80% power. To achieve this number of events, it was estimated that approximately 2000 patients would need to be recruited.

Median follow-up was calculated using the reverse Kaplan–Meier estimator (17). Analyses were according to the intention-to-treat principle, included all randomly assigned patients, and were performed using STATA 8.0 (18). Overall survival was defined as time from date of random assignment to date of death. Relapse-free survival was defined as time from date of random assignment to date of first recurrence or death from breast cancer with no known date of relapse. In the relapse-free survival analysis, patients were censored on the occasion of an intercurrent death. Cumulative survival curves were constructed as Kaplan–Meier time-to-event plots (17), with unadjusted comparisons between groups based on the log-rank test (two-sided). Cox regression models were used to

estimate treatment effects, with adjustment for age, nodal status, and ER status. Proportionality of hazards was verified according to Schoenfeld residuals. Estimates of treatment effect are presented as hazard ratios (HRs) with their associated 95% confidence intervals (CIs). Hazard ratios of less than 1.0 show a benefit to the addition of chemotherapy. Descriptive subgroup analyses for overall survival by age and menopausal status with and without ovarian ablation or suppression are presented as forest plots. Chi-square tests (for trend if appropriate) were used to test for heterogeneity between subgroups. Results for the Quality of Life study are based on complete data available to 30 months. These longitudinal data were analyzed by general linear models for panel data using the generalized estimating equations approach (19) via the xtgee command in STATA 8.0.

Results

Between December 4, 1992, and October 2, 2000, 1991 patients from 106 centers in the United Kingdom and 16 outside the United Kingdom were entered into the ABC (CT) Trial (Fig. 1). Twenty-one patients (11 allocated chemotherapy, 10 allocated no chemotherapy) were subsequently deemed to be ineligible due to stage (3b or 4, n = 14), previous other cancer (n = 4), inadequate consent (n = 2), or physician notification (n = 1). Baseline characteristics were well balanced across the two groups (Table 1). In all, 1244 (62%) patients were older than 50 years, and 1075 (57% of the 1893 with known nodal status) had node-positive disease. Seven hundred fifty-one (38%) patients had ER+ tumors, 424 (21%) had ER– tumors, and tumors of 816 (41%) had unknown ER status. Of women younger than 50 years, 35% were node positive; of women aged 50 years and older, 63% were node positive (% based on those with known nodal status).

Analysis was based on follow-up received by the trials units to June 30, 2004. At this time, 10623 women-years of follow-up had accrued. Median follow-up was 6.4 years (interquartile range [IQR] = 4.8–8.1 years). Completeness of follow-up was 81.4% (20).

Of the 987 patients randomly assigned to chemotherapy, 907 (92%) received one or more cycles of polychemotherapy; of these,

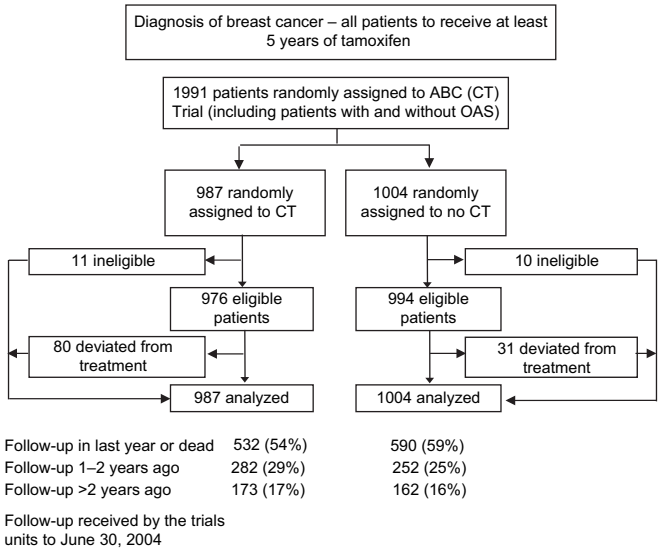


Fig. 1. CONSORT flow chart of the Adjuvant Breast Cancer Chemotherapy (ABC [CT]) Trial. Percentages may not add to 100 due to rounding. OAS = ovarian ablation or suppression.

Table 1. Baseline patient and tumor characteristics and primary treatment details of patients enrolled in the Adjuvant Breast Cancer Chemotherapy Trial

Variable	Chemotherapy (N = 987)	No chemotherapy (N = 1004)
Age in y at random assignment, mean ± standard deviation	53.6 ± 9.3	53.4 ± 9.2
Age in y, No. (%)		
<40	79 (8.0)	72 (7.2)
40–49	233 (23.6)	256 (25.5)
50–59	397 (40.2)	402 (40.0)
60–69	252 (25.5)	248 (24.7)
≥70	26 (2.6)	26 (2.6)
Country, No. (%)		
United Kingdom	581 (58.9)	597 (59.5)
India	211 (21.4)	213 (21.2)
Iran	56 (5.7)	57 (5.7)
Sri Lanka	73 (7.4)	73 (7.4)
Egypt	31 (3.1)	30 (3.0)
Malta	10 (1.0)	12 (1.2)
Saudi Arabia	10 (1.0)	8 (0.8)
Singapore	7 (0.7)	8 (0.8)
Pakistan	6 (0.6)	5 (0.5)
New Zealand	2 (0.2)	1 (0.1)
Tumor size, No. (%)		
<2 cm	396 (40.1)	393 (39.1)
2–5 cm	463 (46.9)	467 (46.5)
>5 cm	61 (6.2)	76 (7.6)
Unknown	67 (6.8)	68 (6.8)
Nodal status, No. (%)		
Negative	404 (40.9)	414 (41.2)
1–3 positive nodes	358 (36.3)	373 (37.2)
≥4 positive nodes	161 (16.3)	142 (14.1)
Positive—unknown number	19 (1.9)	22 (2.2)
Unknown	45 (4.6)	53 (5.3)
Histologic type, No. (%)		
Infiltrating ductal	857 (86.8)	883 (87.9)
Infiltrating lobular	75 (7.6)	57 (5.7)
Other	55 (5.5)	64 (6.4)
Estrogen receptor status,* No. (%)		
Positive	355 (36.0)†	396 (39.4)†
Negative	218 (22.1)	206 (20.5)
Unknown	414 (41.9)	402 (40.0)
Type of surgery, No. (%)		
Mastectomy	625 (63.3)	636 (63.3)
Excision	343 (34.8)	353 (35.2)
Other	19 (1.9)	15 (1.5)
Breast radiotherapy, No. (%)	647 (65.6)	685 (68.2)
Ovarian ablation/ suppression, No. (%) (premenopausal women only)	121 (12.3)	123 (12.3)

* Data for positive and negative estrogen receptor status include retrospectively ascertained status for some patients whose data were unknown at random assignment.

† Percentage of those with known receptor status was 62.0% (chemotherapy group) and 65.8% (no-chemotherapy group).

Table 2. Treatment of patients in the Adjuvant Breast Cancer Chemotherapy Trial who were randomly assigned to chemotherapy*

Category	N (%)
Received chemotherapy as planned	
Full course	433 (44)
With delays	220 (22)
With modifications	105 (11)
Did not receive chemotherapy as planned	
Did not start	80 (8)
Stopped prematurely	149 (15)
Toxic effects†	60 (40)
Patient choice	40 (27)
Deterioration/progression	10 (7)
Other	16 (11)
Not known	23 (15)
Total	987 (100)

* Women with early-stage breast cancer were enrolled in the trial and were to receive long-term (≥5 years) tamoxifen treatment.

† Clinician reported.

Table 3. Endpoint events in the Adjuvant Breast Cancer Chemotherapy Trial

Variable	Chemotherapy (N = 987)	No chemotherapy (N = 1004)
Events included in analysis of relapse-free survival, No.		
Local recurrence only	21	13
Local and distant recurrence	59	70
Distant recurrence only	218	249
Second primary cancer, No.		
Breast	15	17
Endometrial	7	5
Other gynecologic (ovary, cervix)	1	3
Gastrointestinal (colon, rectum, etc.)	4	6
Acute myeloid leukemia	0	2
Other	8	10
Death, No.		
Any cause	243	282
Breast cancer-related	217	264
Intercurrent (without recurrence)	26	18
Vascular causes	3	2
Cardiac causes	6	6
Thrombotic causes	3	2
Pulmonary causes	3	1
Chemotherapy toxicity	3	0
Other/unknown cause	8	6

791 (87%) received CMF (37% 4-week Bonnadonna, 11% 4-week classical iv, 23% 3-week Scottish, 17% 3-week iv, 12% other CMF), 102 (11%) received anthracycline-based regimens, and the remaining 14 (2%) received other polychemotherapy regimens. Of the 987 patients, 758 (77%) received the planned number of cycles, and 653 (66%) received all planned cycles at full dose. One hundred forty-nine (15%) patients prematurely discontinued chemotherapy (Table 2).

Among the 92% of patients who received chemotherapy, tamoxifen was given concurrently, and in the remaining 5%, tamoxifen was started after chemotherapy. At the time of analysis, 1409 (71%) patients were no longer taking tamoxifen. Of these, only six never took tamoxifen. Median tamoxifen duration (censoring those patients who stopped tamoxifen treatment due to recurrence) was 5.0 years (IQR = 3.5–5.5 years).

At the time of this analysis, 525 deaths (26% of patients) and 630 recurrences had been reported (Table 3). The unadjusted hazard ratio for relapse during the 10 years of follow-up for patients in the chemotherapy group relative to those in the no-chemotherapy group was 0.89 (95% CI = 0.76 to 1.04, P = .14) (Fig. 2). Five-year relapse-free survival was 72.0% (95% CI = 68.9% to 74.8%) in the chemotherapy group and 69.6% (95% CI = 66.5% to 72.5%) in the group randomly assigned to no chemotherapy (difference = 2.4%, 95% CI = −1.8% to 6.6%). The relapse-free survival curves diverged during the first 5 years but remained roughly parallel thereafter (at 0- to 1-year follow-up, HR = 0.74, 95% CI = 0.52 to 1.04; at 1–5 years, HR = 0.93, 95% CI = 0.77 to 1.13; at ≥5 years, HR = 0.93, 95% CI = 0.62 to 1.40).

The unadjusted hazard ratio for death from any cause among patients in the chemotherapy group compared with the no-chemotherapy group was 0.86 (95% CI = 0.73 to 1.03, P = .09) (Fig. 3). Five-year survival was 78.7% (95% CI = 75.9% to 81.3%) for patients in the chemotherapy group and 77.3% (95% CI = 74.4% to 79.9%) for patients who did not receive chemotherapy (difference = 1.4%, 95% CI = −2.4% to 5.3%). The beneficial effect of chemotherapy on overall survival emerged only after 5 years (at 0- to 1-year follow-up, HR = 1.02, 95% CI = 0.58 to 1.79; at 1–5 years, HR = 0.92, 95% CI = 0.75 to 1.14; at ≥5 years, HR = 0.67, 95% CI = 0.47 to 0.96).

Subgroup analyses were performed to explore the consistency of chemotherapy benefit across different prognostic groups. The magnitude of the chemotherapy benefit on overall survival may be related to age at random assignment (Fig. 4) and to menopausal status and use of ovarian suppression (Fig. 5), although differences in overall survival between premenopausal subgroups who did or did not receive ovarian ablation or suppression were not statistically significant. Adjusting for use of ovarian suppression, as

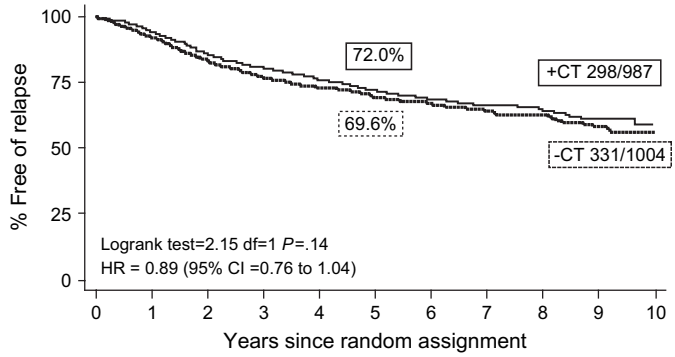
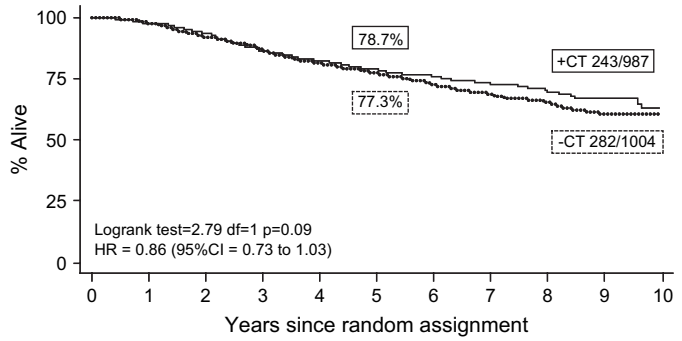


Fig. 2. Relapse-free survival of patients in the Adjuvant Breast Cancer Chemotherapy Trial. Patients who received chemotherapy (+CT, **solid line**) and those who received none (–CT, **hatched line**). HR = hazard ratio for relapse in the chemotherapy versus no-chemotherapy groups; CI = confidence interval; df = degrees of freedom. P value (two-sided) calculated using log-rank test.



No. of events/No. at risk

-CT	1004	24/959	56/881	50/799	48/679	30/554	31/418	20/297	11/177	10/68	0/11
+CT	987	24/944	40/875	65/768	33/671	28/553	20/418	14/308	10/191	6/88	2/18

Fig. 3. Overall survival of patients in the Adjuvant Breast Cancer Chemotherapy Trial. Patients who received chemotherapy (+CT, **solid line**) and those who received none (–CT, **hatched line**). HR = hazard ratio for all-cause mortality in the chemotherapy versus no-chemotherapy groups; CI = confidence interval; df = degrees of freedom. *P* value (two-sided) calculated using log-rank test.

opposed to tamoxifen treatment alone, did not materially alter the estimate of chemotherapy effect on overall survival (HR = 0.86, *P* = .06); in addition, the interaction test was not statistically significant (*P* = .83).

Adjusting for age, nodal status, and ER status had little effect on the hazard ratios for both overall and relapse-free survival (Table 4). There was no statistically significant evidence of heterogeneity for either overall or relapse-free survival among any subgroups investigated (data not shown). However, chemotherapy appeared to have less of an effect in the centers outside the United Kingdom (UK patients: overall survival, HR = 0.81, 95% CI = 0.65 to 1.02; *P* = .07; relapse-free survival, HR = 0.81, 95% CI = 0.66 to 1.00; *P* = .05; non-UK patients: overall survival, HR = 0.94, 95% CI = 0.72 to 1.23; *P* = .70; relapse-free survival, HR = 1.00, 95% CI = 0.79 to 1.28; *P* = .98).

Of the 1178 UK patients who were included in the ABC (CT) Trial, 199 (103 with chemotherapy, 96 no chemotherapy) agreed

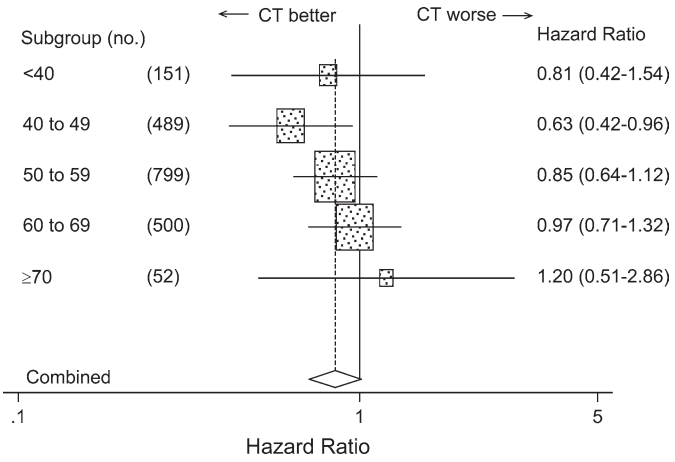


Fig. 4. Subgroup analysis of overall survival by age group (in years) of patients in the Adjuvant Breast Cancer Chemotherapy Trial. The **size of the boxes** is proportional to the number of events in the subgroup. Hazard ratios for all-cause mortality in the chemotherapy versus no-chemotherapy groups (with 95% confidence intervals) are shown. CT = chemotherapy.

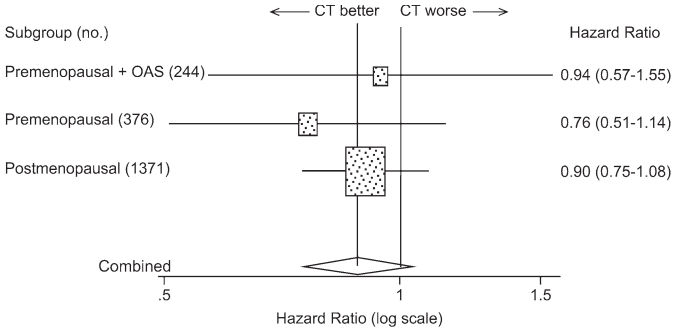


Fig. 5. Subgroup analysis of overall survival by menopausal status and receipt of ovarian ablation or suppression (OAS) of patients in the Adjuvant Breast Cancer Chemotherapy Trial. The **size of the boxes** is proportional to the number of events in the subgroup. Hazard ratios for all-cause mortality in the chemotherapy versus no-chemotherapy groups (with 95% confidence intervals) are shown. CT = chemotherapy.

to take part in the quality of life substudy, and detailed results will be published elsewhere. In summary, as expected, patients who received chemotherapy recorded more side effects for the first 9 months after random assignment than patients who did not receive chemotherapy (data not shown), reflecting the period during and shortly after treatment. In addition, patients who received chemotherapy also reported more problems associated with chronic effects, particularly those relating to vasomotor menopausal symptoms, e.g., night sweats, than patients who did not receive chemotherapy (*P* = .02) (Fig. 6).

Discussion

Compared with no chemotherapy, chemotherapy in combination with 5 years of tamoxifen treatment produced modest improvements in relapse-free and overall survival. Relapse-free survival benefits emerged early and were maintained, whereas overall survival benefits did not emerge for at least 5 years, reinforcing the need for long-term follow-up in chemotherapy trials. The ABC (CT) Trial results are consistent with the independence of chemotherapy and tamoxifen effects (21).

Subgroup analyses revealed that the benefit of chemotherapy appeared greatest in those treated in the United Kingdom. The reason for this result is not understood because it is not explained by differences in standard prognostic factors or chemotherapy regimen or compliance. In particular, the type of CMF used in the United Kingdom and elsewhere, and the doses administered, did not differ substantially. Differences in tumor ER expression between countries could not be tested because this information was not available outside the United Kingdom. The apparent difference merits further study, especially of the biology of the disease in these different populations and of possible differences in drug metabolism. If confirmed, it would have important implications for the treatment of women with early breast cancer in some countries.

The study has several potential limitations. One is that in the many years it has taken to gather mature survival data for the ABC (CT) Trial, our knowledge underpinning breast cancer treatment has grown. The latest overview shows that compared with CMF, anthracycline-containing chemotherapy offers a moderate

Table 4. Outcomes in the chemotherapy group as compared with the no-chemotherapy group*

Endpoint	Unadjusted hazard ratio (95% CI)	*P*	Adjusted hazard ratio (95% CI)	*P*
Relapse	0.89 (0.76 to 1.04)	.14	0.86 (0.73 to 1.01)	.06
Death from any cause	0.86 (0.73 to 1.03)	.09	0.83 (0.70 to 0.99)	.03

* A Cox model including age (<50 or ≥50 years), nodal status (negative, 1–3 positive nodes, ≥4 positive nodes, or missing), and estrogen receptor status (positive, negative, or missing) was used to estimate the adjusted hazard ratios. CI = confidence interval. *P* values (two-sided) were determined by using the log-rank test for the unadjusted hazard ratios and the Wald test from Cox regression for the adjusted hazard ratios.

but statistically significant advantage in terms of recurrence (rate ratio = 0.89; $P = .001$) and breast cancer death (rate ratio = 0.84; $P<.001$) (21). The recent National Epirubicin Adjuvant Trial has concluded that CMF used in sequence with epirubicin (E-CMF) is superior to CMF alone (22). Other recent trials have also reported superiority for taxane-containing regimens (23–27).

Although CMF is no longer the chemotherapy of choice in adjuvant breast cancer, these drugs form a major component of some of today's preferred regimens, e.g., E-CMF (21). In addition, CMF is still widely used in some countries (28), in part because it is more cost effective than newer regimens.

A second potential limitation relates to dose intensity. In a systematic review (29), trials comparing anthracyclines or "classical" CMF schedules in combination with tamoxifen yielded better outcomes than tamoxifen alone, whereas trials using "modified" CMF regimens showed no benefit (29,30). Data from a small study of 104 patients (31) suggested that when AC and CMF are given at equitoxic doses, there is no difference in disease-free survival (AC, DFS = 67%; CMF, DFS = 69%; $P = .89$). In the ABC (CT) Trial, despite the recommendation that the Bonnadonna CMF regimen be used, a variety of CMF regimens were used, potentially affecting the magnitude of benefit observed. Minimal data collection in the ABC (CT) Trial precludes detailed dose intensity analysis, but the available data suggest that, in centers where the majority of patients received all cycles at full dose, patients had better relapse-free and overall survival than those who did not receive all cycles at full dose (data not shown).

Third, tamoxifen was given to all patients, regardless of ER status. Although not standard practice today, no bias has been introduced into the evaluation of chemotherapy because the proportion of patients with ER– tumors was similar in both arms.

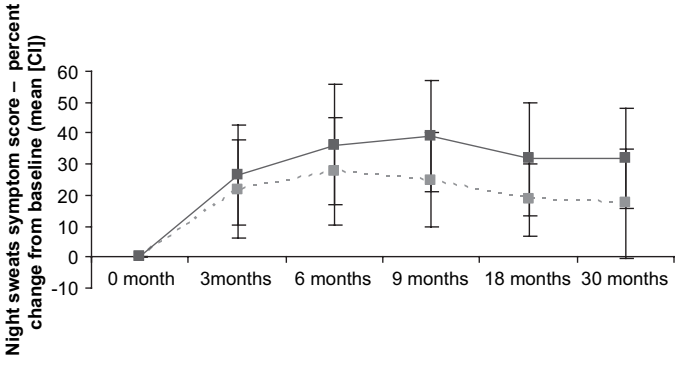


Fig. 6. Change from baseline in night sweats symptom score according to receipt of chemotherapy (CT) of patients in the Adjuvant Breast Cancer Chemotherapy Trial. Patients who received chemotherapy (+CT, **solid line**) and those who received none (−CT, **hatched line**). Means and 95% confidence intervals (CI) are shown.

Tamoxifen was also given concurrently with chemotherapy, which was standard practice in the United Kingdom and other countries at the time. More recently, a substantial benefit for sequential versus concurrent chemoendocrine therapy has been reported, so our trial results may underestimate chemotherapy effect (32).

The finding that patients younger than 40 years benefited less from chemotherapy than those in the 40- to 49-year age group (Fig. 4) may be due to chance, but it is consistent with the 2005 EBCTCG overview of the effects of polychemotherapy in women with ER+ tumors (21). The following observations may be important to the low likelihood (generally <50%) of ovarian suppression by chemotherapy in women younger than age 40 years. First, there was some evidence (albeit non–statistically significant) (Fig. 5) that premenopausal women may benefit less from chemotherapy against a background of ovarian ablation (usually delivered after chemotherapy by radiation or surgery) than those premenopausal women who did not receive ovarian ablation or suppression. Second, although all patients received tamoxifen (and a minority ovarian ablation as well), there was clear evidence of an effect of chemotherapy on ovarian function in premenopausal women, in that vasomotor symptoms were twice as severe in this subgroup as compared with the corresponding no-chemotherapy group (Fig. 6). These data are consistent with a model in which polychemotherapy mediates a large part of its effects in premenopausal women via chemical castration, as demonstrated by the International Breast Cancer Study Group (IBCSG) Trial VIII (33–35).

One of the characteristics of breast cancer is that tumors continue to recur for at least 10 years after diagnosis (36). The updated EBCTCG overview (21), which extends results to 15 years, has provided clarity on the long-term benefits associated with tamoxifen, chemotherapy, and ovarian ablation but includes few trials in which chemotherapy has been evaluated in the presence of prolonged tamoxifen. Although the ABC (CT) Trial has collected more than 10 000 women-years of follow-up with a median follow-up of 6.4 years, it is likely that the true impact of the addition of chemotherapy on overall survival benefit is only just emerging.

The benefit of chemotherapy plus tamoxifen involves a trade-off between acute and chronic side effects. As expected, the Quality of Life substudy showed that chemotherapy had an impact on many side effects during treatment, including nausea and vomiting, dyspnea, constipation, fatigue, and insomnia. These problems generally returned to baseline values within 9 months of random assignment, but there was also a continued excess of chronic problems in the chemotherapy arm, particularly menopausal symptoms in premenopausal women. Explicit discussion with patients about the potential benefits and side effects is therefore critical.

The ABC Trials established a collaborative network for breast cancer trials in the United Kingdom, which has also conducted other successful systemic therapy trials, such as the Taxotere as Adjuvant Chemotherapy (TACT) Trial (37). In addition, collaboration with the international centers has helped in the development of a research infrastructure where it did not previously exist.

References

(1) Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. 133 randomized trials involving 31000 recurrences and 24000 deaths 75000 women. Lancet 1992;339:1–15, 71–85.

(2) Clemons M, Danson S, Howell A. Tamoxifen ('Nolvadex'): a review. Cancer Treat Rev 2002;28:165–80.

(3) Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer. Vol 1.: Worldwide evidence 1985–1990. Oxford: Oxford University Press; 1990.

(4) Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976;294:405–10.

(5) Kerr DJ, Earl HM, Baker PG, Jevons CM, Lee MJ, Baum M, et al. aTTom—adjuvant tamoxifen treatment, offer more? Br J Cancer 1996; 74(Suppl):528.

(6) Peto R. Five years of tamoxifen—or more? [editorial]. J Natl Cancer Inst 1996;88:1791–3.

(7) Jasani B, Douglas-Jones A, Rhodes A, Wozniak S, Barrett-Lee P, Gee J, et al. Measurement of estrogen receptor status by immunocytochemistry in paraffin wax sections. Methods Mol Med 2006;120:127–46.

(8) Barnes DM, Harris WH, Smith P, Millis RR, Rubens RD. Immunohistochemical determination of estrogen receptor: comparison of different methods of assessment of staining and correlation with clinical outcome of breast cancer patients. Cancer 1996;74:1445–51.

(9) Fisher B, Brown AM, Dimitrov NV, Poisson R, Redmond C, Margolese RG, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen nonresponsive tumours: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990;8: 1483–96.

(10) Pritchard KI, Paterson AH, Paul NA, Zee B, Fine S, Pater J. Increased thromboembolic complications with concurrent tamoxifen and chemotherapy in a randomized trial of adjuvant therapy for women with breast cancer. National Cancer Institute of Canada Clinical Trials Group Breast Cancer Site Group. J Clin Oncol 1996;14:2731–7.

(11) Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. QLQ-C30: a quality-of-life instrument for use in International Clinical Trials in Oncology. J Natl Cancer Inst 1993;85:365–76.

(12) Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14: 2756–68.

(13) Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.

(14) Thirlaway K, Fallowfield L, Cuzick J. The sexual activity questionnaire: a measure of women's sexual functioning. Qual Life Res 1996;5:81–90.

(15) Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. Br Med J 1998;316:736–41.

(16) Fayers PM, Aaronson NK, Bjordal K, Curran D, Groenvold M. EORTC Quality of Life Study Group. EORTC QLQ-C30 scoring manual. 3rd ed. Brussels (Belgium): EORTC Quality of Life Group; 2001. p. 86.

(17) Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–81.

(18) StataCorp. Stata statistical software: release 8.0. College Station (TX): Stata Corporation; 2003.

(19) Liang K-Y, Zegler SL. Longitudinal data analysis using generalised linear models. Biometrika 1986;73:13–22.

(20) Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. Lancet 2002;359:1309–10.

(21) Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet 2005;365: 1687–717.

(22) Poole CJ, Earl HM, Hiller L, Dunn JA, Bathers S, Grieve RJ, et al. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. N Engl J Med 2006;355: 1920–2.

(23) Henderson C, Berry DA, Demetri GD, Cirrincione CT, Goldstein LJ, Martino S, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21:976–83.

(24) Martin M, Rodriguez-Lescure A, Ruiz A, Alba E, Calvo L, Ruiz-Borrego M, et al. Multicenter, randomized phase III study of adjuvant chemotherapy for node-positive breast cancer comparing 6 cycles of FEC versus 4 cycles of FEC followed by 8 weekly paclitaxel administrations: interim analysis of GEICAM 9906 trial. Breast Cancer Res Treat 2005; 94(Suppl 1):S20.

(25) Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Weaver C. TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up. Breast Cancer Res Treat 2003;82(Suppl 1).

(26) Roche H, Fumoleau P, Spielman M, Canon JL, Delozier T, Kerbrat P, et al. Five years analysis of the PAC01 trial: 6 cycles of FEC 100 versus 3 cycles of FEC 100 followed by 3 cycles of docetaxel for the adjuvant treatment of node positive breast cancer. Breast Cancer Res Treat 2004;88 (Suppl 1):A27.

(27) Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: results of North American Breast Cancer Intergroup Trial E1199. San Antonio Breast Cancer Symposium 2005 (December 8–11); Abstract 038.

(28) Prozato P, Cazzaniga ME, Mustacchi G, Di Costanzo F, de Matteis A, Pareu L, et al. Applications of new adjuvant treatments for node positive (N+) breast cancer (BC) patients (pts) in Italian centres. Results of the NORA (National Oncological Research Observatory on Adjuvant Therapy in Breast Cancer) Study. Proc Am Soc Clin Oncol 2005; 24:abstract 878).

(29) Colleoni M, Coates A, Pagani O, Goldhirsch A. Combined chemoendocrine adjuvant therapy for patients with operable breast cancer: still a question?. Cancer Treat Rev 1998;24:15–26.

(30) Goldhirsch A, Colleoni M, Coates AS, Castiglione-Gertsch M, Gelber RD. Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: are all CMFs alike? The International Breast Cancer Study Group (IBCSG). Ann Oncol 1998;9:489–93.

(31) Pribylova O, Petruzelka LB, Shumansky K, Spinelli JJ, Ragaz J. Randomized trial of adjuvant equitoxic dose-escalated anthracycline (A)-containing regimen of doxorubicin, cyclophosphamide (AC) versus cyclophosphamide, methotrexate, 5FU (CMF) for stage I-II breast cancer (BrCa): can equitoxicity compensate for agent selection?. Proc Am Soc Clin Oncol 2005;24:abstract 818.

(32) Albain K, Barlow W, O'Malley F, Siziopikou K, Yeh I-T, Ravdin P, et al. The Breast Cancer Intergroup of North America. Concurrent (CAFT) versus sequential (CAF-T) chemohormonal therapy (cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen) versus T alone for postmenopausal, node-positive, estrogen and/or progesterone receptor-positive breast cancer: mature outcomes and new biologic correlates on phase III intergroup trial 0100 (SWOG-8814). San Antonio Breast Cancer Symposium 2004 (December 8–11).

(33) Castiglione-Gertsch M. Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node–negative breast cancer: a randomized trial. The International Breast Cancer Study Group (IBCSG). J Natl Cancer Inst 2003;95:1833–46.
(34) Pagani O, O'Neill A, Castiglione M, Gelber RD, Goldhirsch A, Rudenstam C, et al. Prognostic impact of amenorrhoea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement: results of the International Breast Cancer Study Group (IBCSG) Trial VI. Eur J Cancer 1998;34:632–640.
(35) Jordan VC. Chemotherapy is antihormonal therapy—how much proof do oncologists need? Eur J Cancer 1998;34:606–8.
(36) Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 1996;14:2738–46.
(37) Barrett-Lee P, Ellis P, Bliss J. TACT Trial Management Group. Duration of adjuvant chemotherapy; anthracyclines, taxanes and novel agents-more or less. Clin Oncol (R Coll Radiol) 2002;14:263–6.

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