Patients with Slowly Proliferative Early Breast Cancer Have Low Five-Year Recurrence Rates in a Phase III Adjuvant Trial of Capecitabine

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Abstract

Purpose: We conducted a randomized phase III study to determine whether patients with early breast cancer would benefit from the addition of capecitabine (X) to a standard regimen of doxorubicin (A) plus cyclophosphamide (C) followed by docetaxel (T).

Experimental Design: Treatment comprised eight cycles of AC—T (T dose: 100 mg/m2 on day 1) or AC—XT (X dose: 825 mg/m2 twice daily, days 1–14; T dose: 75 mg/m2 on day 1). The primary endpoint was 5-year disease-free survival (DFS).

Results: Of 2,611 women, 1,304 were randomly assigned to receive AC—T and 1,307 to receive AC—XT. After a median follow-up of 5 years, the study failed to meet its primary endpoint [HR, 0.84; 95% confidence interval (CI), 0.67–1.05; P = 0.125]. A significant improvement in overall survival, a secondary endpoint, was seen with AC—XT versus AC—T [HR, 0.68; 95% CI, 0.51–0.92; P = 0.011]. There were no unexpected adverse events. Of patients with estrogen receptor (ER)—positive/HER2-negative disease, 70% of whom were node-positive, 26% and 59% had tumors with a centrally assessed Ki-67 score of <10% or <20%, respectively, and only 17 (2%) and 53 (6%) DFS events, respectively, occurred in these groups at 7 years.

Conclusions: The very low event rate in patients with ER-positive, low Ki-67 cancers, regardless of nodal status, strongly suggests that these patients should not be enrolled in adjuvant trials that assess 5-year DFS rates and that central Ki-67 analyses can identify these patients.

Clin Cancer Res; 21(19); 4305–11. © 2015 AACR.

Introduction

Combination regimens incorporating anthracyclines/taxanes are among the most effective for early breast cancer (EBC) and are particularly suitable for high-risk, node-positive disease (1–3). Incorporation of taxanes into (neo)adjuvant chemotherapy regimens for high-risk EBC is recognized as the standard-of-care on the basis of improvements in overall survival (OS), recurrence-free survival (RFS), and disease-free survival (DFS; refs. 4–8).

Given the hypothesis of a lesser benefit of adjuvant chemotherapy in indolent breast cancer, investigators have searched for molecular markers that may predict response to treatment, with a number of studies indicating a role for Ki-67 (9–12). In a retrospective analysis of the Breast Cancer International Research Group 001 trial, significantly improved 3-year DFS was observed with docetaxel (T) plus doxorubicin (A) plus cyclophosphamide (C) versus fluorouracil (F) plus AC in patients with luminal B tumors [estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive and HER2-positive or Ki-67 ≥ 13%: HR, 0.66; 95% confidence interval (CI), 0.46–0.95; P = 0.025]. However, this was not observed in patients with luminal A tumors (ER- and/or PgR-positive, HER2-negative, Ki-67 < 13%: HR, 0.70; 95% CI, 0.27–1.83; P = 0.472; ref. 11). Similarly, in a biomarker study of patients receiving adjuvant epirubicin (E) plus FC—T versus FEC, the HR for DFS was 0.51 (95% CI, 0.26–1.01) in ER-positive/Ki-67 > 20% tumors versus 1.03 (95% CI, 0.69–1.55) in ER-positive/Ki-67 ≤ 20% tumors (12).

Capecitabine (X) is an attractive agent for use in combination regimens owing to its synergism with docetaxel (13) and minimal overlapping toxicity (14). The capecitabine plus docetaxel (XT) combination demonstrated significantly superior time to progression and OS versus docetaxel alone in the pivotal phase III metastatic breast cancer trial (15, 16).

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

In agreement with studies reporting a lack of benefit with the addition of capecitabine (X) to (neo)adjuvant chemotherapy, this randomized phase III trial failed to demonstrate a disease-free survival (DFS) benefit with doxorubicin (A) plus cyclophosphamide (C) followed by X plus docetaxel (T) (AC—XT) versus AC—T after a median follow-up of 5 years. A significant improvement in overall survival was observed. No DFS benefit with X was seen by central Ki-67 analyses overall or in estrogen receptor (ER)-positive/HER2-negative tumors. Exploratory analyses suggested benefit from X in lobular early breast cancer. The power of the study was decreased because of a lower-than-expected number of DFS events, despite 70% of patients having node-positive disease. These data indicate that patients with indolent ER-positive, low Ki-67 cancers have a very low recurrence risk and therefore should not be enrolled in adjuvant trials assessing 5-year DFS rates.

Materials and Methods

Study design

This was an open-label, randomized, phase III study of adjuvant AC—T versus AC—XT in high-risk EBC (ClinicalTrials.gov: NCT00089479). The study was carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of each investigational site. Patients provided written informed consent before any study-related procedure.

Patients

Women aged ≥18 and <70 years with high-risk (T1–3, N1–2, M0; or T ≥2 cm, N0, M0; or T > 1 cm, N0, M0 and both ER- and PgR-negative), operable, histologically confirmed adenocarcinoma of the breast were eligible. Known ER, PgR, menopausal status, and a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 were required.

Randomization and masking

Patients were randomized 1:1 between treatment arms centrally by USO Research Center (Houston, TX). Randomization was stratified according to number of positive lymph nodes (0 vs. 1 to 3 vs. ≥4), ER/PgR status (negative vs. positive), and menopausal status (pre vs. post). Tumors were classified as both ER-negative and PgR-negative if they had <10% nuclear staining for each receptor. Postmenopausal patients with hormone receptor-positive disease were further stratified by hormonal therapy (tamoxifen followed by aromatase inhibitor vs. aromatase inhibitor alone).

Initially, an X dose of 950 mg/m² twice daily was chosen to mirror the median delivered dose in the registration study (14). Owing to unacceptable levels of stomatitis and X dose reductions and discontinuations at the interim safety analysis, the dose was lowered to 825 mg/m² twice daily.

Treatment comprised 8 cycles of AC—T (four 3-weekly cycles of A 60 mg/m² intravenously on day 1 plus C 600 mg/m² intravenously on day 1, then four 3-weekly cycles of T 100 mg/m² intravenously on day 1) or AC—XT (four 3-weekly cycles of AC, then four 3-weekly cycles of X 825 mg/m² orally twice daily on days 1 to 14 plus T 75 mg/m² intravenously on day 1). Dose modifications were permitted for grade ≥2 treatment-related adverse events according to National Cancer Institute-Common Terminology Criteria version 2. Patients with hormone receptor-positive disease received tamoxifen, an aromatase inhibitor, or both, sequentially, for 5 years. After 2005, patients with HER2-positive disease were offered 1 year of concurrent or post-study trastuzumab. HER2 status was assessed in local pathology laboratories and deemed positive or negative on the basis of local standards at the time of diagnosis.

Study assessments

The primary objective was to compare DFS with AC—T versus AC—XT (from randomization until recurrence or death, whichever occurred first). Secondary objectives were to compare OS between the regimens (from randomization until death) and safety. Additional endpoints included DFS1 (time to recurrent disease, new primary breast cancer, or death); DFS2 (time to recurrent disease, new primary cancer, or death); and breast cancer–free survival (BCFS: time to recurrent disease, new primary breast cancer, or death due to breast cancer or related to study chemotherapy). Exploratory analyses were conducted for distant DFS (systemic recurrences and deaths), invasive DFS (excludes ductal carcinoma in situ), DFS according to centrally assessed Ki-67 status, and the efficacy of X in ductal versus lobular or mixed lobular/ductal EBC. Central Ki-67 immunohistochemistry was performed using the SP6 monoclonal antibody and read by a pathologist who was blinded to all clinical data, according to published recommendations (17).

Statistical analysis

The primary analysis was based on the intent-to-treat (ITT) population, which comprised all randomized patients. The per-protocol population excluded patients who did not receive at least 2 cycles of both AC and T in the AC—T arm or at least 2 cycles of both AC and XT with ≥50% of the planned dose of X (unless because of recurrent disease or death) in the AC—XT arm. The safety population comprised all patients who received at least one dose of any study drug and had at least one safety follow-up measure. All patients were to be followed for 6 years after the completion of chemotherapy, including assessment of disease recurrence, toxicity, and survival status. The planned sample size of 2,410 was based on a 5-year DFS rate of 73.2% for AC—T, an HR of 0.78, and one interim analysis. An additional 200 patients were required when adjuvant trastuzumab was permitted for HER2-positive disease, giving a total of 2,610 patients.

A low event rate triggered amendment of the statistical analysis plan from event-driven to time-driven (median follow-up of 5 years) without interim analysis; this lowered the power of the study to 57% to show superiority of the AC—XT arm (assuming a 5-year DFS for AC—T of 89.4% and HR of 0.78). Final OS analyses were conducted 2 years after the primary DFS analysis. Database lock was August 10, 2012.
Low Five-Year Recurrences in ER-Positive, Low Ki-67 Cancers

Results

Patients

Between August 2002 and February 2006, 2,611 women were randomized to receive AC→T (n = 1,304) or AC→XT (n = 1,307; Fig. 1). Primarily owing to protocol-defined insufficient delivered doses (see Fig. 1 for definitions), 121 patients were excluded from the per-protocol population in the AC→T arm and 413 in the AC→XT arm. Patients receiving XT could discontinue X and continue T for 4 cycles and be included in the per-protocol population. Thus, the large number of patients excluded from the per-protocol population in the XT arm was mainly as a result of early toxicity-related X discontinuations.

The treatment arms were balanced at baseline (Table 1). Median patient age was 51 years (range, 26–72). Just more than half of the patients had hormone receptor–positive disease (ER- and PgR-positive) and almost 13% had HER2-positive disease. Approximately 30% of patients had triple-negative breast cancer (TNBC) as defined as <10% nuclei positive for ER and PgR.

Median total dose intensity for T was 0.97 (range, 0.08–1.41) in the AC→T arm and 0.96 (range, 0.03–1.45) in the AC→XT arm. Median total dose intensity for X was 0.67 (range, 0–1.20). On the XT arm, 95.6% of patients received 1 cycle of X, 85.8% received 2 cycles, 78.6% received 3 cycles, and 68.7% received 4 cycles.

All survival endpoints were analyzed using Cox proportional hazards regression models and presented as Kaplan–Meier estimates with HR and 95% CI. Treatment arms were compared using a 2-sided log-rank test. Subpopulation treatment effect pattern plot (STEP) analysis compared 5-year DFS between the treatment arms within predefined patient subgroups based on Ki-67 levels.

Efficacy

After a median follow-up of 5 years, 304 DFS events occurred in the ITT population [164 with AC→T (12.6%) and 140 with AC→XT (10.7%)]. The primary endpoint, improvement in DFS with AC→XT versus AC→T, was not met (HR, 0.84; 95% CI, 0.67–1.05; P = 0.125; Fig. 2A). However, a significant improvement in OS was seen in the AC→XT arm versus the AC→T arm (HR, 0.68; 95% CI, 0.51–0.92; P = 0.011), with 183 events (Fig. 2B). Results of the additional DFS endpoints were consistent with the primary outcome (DFS1: HR, 0.90; 95% CI, 0.72–1.12; P = 0.325; DFS2: HR, 0.87; 95% CI, 0.71–1.06; P = 0.168; BCFS: HR, 0.90; 95% CI, 0.72–1.12; P = 0.343). The per-protocol population analyses showed DFS results similar to those in the ITT population (HR, 0.86; 95% CI, 0.67–1.07; P = 0.235).

The 7-year follow-up analysis confirmed results of the primary analysis. After a median follow-up of 6.4 years, a nonsignificant improvement in DFS was observed with AC→XT versus AC→T.
Central Ki-67 assessment and treatment outcomes

Hypothesis-generating analyses of local pathology-assessed Ki-67 suggested benefit from the addition of X in patients with more highly proliferative tumors (i.e., Ki-67 ≥ 10%; ref. 18). Exploratory central pathology-assessed Ki-67 analyses were performed on archival formalin-fixed, paraffin-embedded primary breast cancer tissue available from 1,514 patients. Prognostic tumor characteristics of these patients were very similar to the overall ITT population (Supplementary Table S1). Ki-67 scores in ER-positive/HER2-negative tumors uncommonly exceeded 40%, whereas TNBC showed a bimodal distribution with peaks around 30% and 80% (Supplementary Fig. S2). Central and local Ki-67 scores were concordant in 63% of patients, with greater agreement at Ki-67 ≥ 20% (Fig. 3; Supplementary Table S2). In a retrospective, exploratory analysis, when using 25th percentiles as the cutoffs, higher Ki-67 levels predicted worse DFS across the pooled treatment arms in patients with ER-positive/HER2-negative tumors (HR, 1.99; P = 0.011) and better DFS in patients with TNBC (HR, 0.55; P < 0.011). Binary cutoffs of 10% and 20% for central Ki-67 did not identify a subpopulation that might achieve significant DFS benefit from X. When analyzing Ki-67 as a continuous variable, X appeared to improve 5-year DFS in ER-positive/HER2-negative tumors (HR, 0.55; P = 0.011) and OS (HR, 0.38; P = 0.0061), with 346 DFS events.

In planned subgroup analyses based on nodal and ER status, among other factors, there were no significant differences in DFS with AC–XT compared with AC–T (Supplementary Fig. S1A). OS benefit with X was seen in patients with node-positive, HER2-negative, and triple-negative disease (Supplementary Fig. S1B). Exploratory analyses of distant DFS demonstrated a HR of 0.80 (95% CI, 0.63–1.02; P = 0.067), with 10.1% of patients with events in the AC–T arm and 7.9% in the AC–XT arm. Systemic recurrent disease was more frequent with AC–T than with AC–XT (11.1% vs. 8.8%, respectively; Table 2).

Table 2. New breast cancer recurrences (ITT population)

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>AC–T (N = 1,304)</th>
<th>AC–XT (N = 1,307)</th>
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<tbody>
<tr>
<td>Systemic recurrent disease, n (%)</td>
<td>145 (11.1)</td>
<td>115 (8.8)</td>
</tr>
<tr>
<td>Bone</td>
<td>64 (4.9)</td>
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<td>In-breast recurrence, n (%)</td>
<td>10 (0.8)</td>
<td>18 (1.4)</td>
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<tr>
<td>New primary breast cancer, n (%)</td>
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Safety

The frequency of treatment-related adverse events (39.7% vs. 100%), grade 3/4 adverse events (88.7% vs. 92.3%), and serious adverse events (20.2% vs. 15.6%) was similar in the AC–T and AC–XT arms, respectively. The most frequent serious adverse event was febrile neutropenia (9% and 6% of patients, respectively). Grade 3 hand–foot syndrome occurred more often with AC–XT (18.1% vs. 3.8%), as did grade 3/4 stomatitis (9.1% vs. 4.5%) and grade 3/4 diarrhea (5.1% vs. 2.9%). Table 3 summarizes the most frequently occurring grade 2–4 adverse events.

Figure 2.

Kaplan–Meier curves of (A) DFS and (B) OS in the ITT population.

(HR, 0.84; 95% CI, 0.68–1.04; P = 0.1136), with 346 DFS events. The follow-up analyses also showed a significant improvement in OS, with 227 OS events (HR, 0.69; 95% CI, 0.53–0.90; P = 0.0061).

In planned subgroup analyses based on nodal and ER status, among other factors, there were no significant differences in DFS with AC–XT compared with AC–T (Supplementary Fig. S1A). OS benefit with X was seen in patients with node-positive, HER2-negative, and triple-negative disease (Supplementary Fig. S1B). Exploratory analyses of distant DFS demonstrated a HR of 0.80 (95% CI, 0.63–1.02; P = 0.067), with 10.1% of patients with events in the AC–T arm and 7.9% in the AC–XT arm. Systemic recurrent disease was more frequent with AC–T than with AC–XT (11.1% vs. 8.8%, respectively; Table 2).

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Overall, 108 patients (8%) in the AC—T arm and 73 patients (6%) in the AC—XT arm died during the study, mostly as a result of recurrent disease. Three deaths were considered treatment-related: 2 during AC (bacterial and neutropenic sepsis) and 1 during XT therapy (bacterial sepsis).

Discussion

This randomized phase III study did not demonstrate an improvement in DFS with AC—XT versus AC—T after a median follow-up of 5 years (304 events) or 7 years (346 events). Results of DFS1, DFS2, BCFS, and DFS in the per-protocol population were consistent with the primary endpoint. Conversely, a significant improvement in OS was observed with AC—XT, with 183 events. Analyses after a median follow-up of 6.4 years confirmed these findings.

Although the lower-than-planned dose intensity of X (due to toxicity) may have contributed to the lack of benefit observed with X, our results are in agreement with studies reporting a lack of clinical benefit with the addition of X to (neo)adjuvant chemotherapy (19–22). In the FinXX study, in high-risk breast cancer, the integration of X into an adjuvant anthracycline/taxane regimen did not significantly improve DFS versus the similar regimen with bolus 5-fluorouracil, although breast cancer—specific survival, but not OS, was significantly improved (19). In the NSABP-B40 trial, the addition of X to T in the context of sequential anthracycline/taxane therapy did not significantly increase pathologic complete response (pCR) versus T alone in operable HER2-negative breast cancer (21). Conversely, in the ABCSG-24 trial, the addition of preoperative X to E and T did significantly improve the pCR rate (23).

Exploratory analyses of distant DFS suggested a treatment effect of X, in contrast to the primary analysis. Thus, the significant OS results may, in part, reflect the lower rate of systemic recurrence in the AC—XT versus AC—T group.

Central Ki-67 analyses showed no differential DFS benefit with X in the overall population or in ER-positive/HER2-negative patients. Concordance in reporting Ki-67 between local and central pathologists was low at 63%, perhaps because Ki-67 results were generally higher with the central use of the SP6 monoclonal antibody versus local use of the MIB1 antibody. Higher Ki-67 conferred worse DFS across the treatment arms in patients with ER-positive/HER2-negative cancers and better DFS in patients with highly proliferative TNBC. Exploratory analysis in FinXX supports the finding of improved DFS with adjuvant X in TNBC (19). Future studies would be required to confirm these hypotheses.

Ductal and lobular cancers have distinct histological, molecular, and natural history characteristics. It remains controversial whether invasive lobular or mixed ductal/lobular breast cancers are as sensitive to (neo)adjuvant chemotherapy as ductal cancers (24–26). Exploratory analyses suggested that patients with lobular/mixed EBC in this study benefited from adjuvant X. This warrants further evaluation in previous adjuvant X trials.

No new safety signals were detected, although there was a higher incidence of grade 3/4 X-related adverse events with AC—XT and a slightly higher incidence of grade 3/4 febrile neutropenia with AC—T than in previously published XT studies. Of note was the high incidence of grade 3/4 stomatitis in the AC—XT arm, most likely related to the use of AC and steroid antiinflammatories immediately before XT. The tolerability of XT was better in NSABP-B40 when these agents were administered before AC (21).

Table 3. Summary of grade 2 to 4 adverse events occurring in ≥15% of patients in any grade in either treatment arm

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>AC—T (N = 1,305)</th>
<th>AC—XT (N = 1,283)</th>
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<tbody>
<tr>
<td></td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>All, n (%)</td>
<td>1,278 (97.9)</td>
<td>929 (71.2)</td>
</tr>
<tr>
<td>Alopecia, n (%)</td>
<td>978 (74.9)</td>
<td>—</td>
</tr>
<tr>
<td>Neutropenia, n (%)</td>
<td>70 (5.4)</td>
<td>167 (12.8)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>—</td>
<td>126 (9.7)</td>
</tr>
<tr>
<td>Stomatitis, n (%)</td>
<td>346 (26.5)</td>
<td>57 (4.4)</td>
</tr>
<tr>
<td>Fatigue, n (%)</td>
<td>462 (35.4)</td>
<td>107 (8.2)</td>
</tr>
<tr>
<td>HFS, n (%)</td>
<td>98 (6.7)</td>
<td>50 (3.8)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>409 (31.3)</td>
<td>72 (5.5)</td>
</tr>
<tr>
<td>Leukopenia, n (%)</td>
<td>75 (5.7)</td>
<td>243 (18.6)</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
<td>166 (12.7)</td>
<td>38 (2.9)</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>254 (19.9)</td>
<td>53 (4.1)</td>
</tr>
<tr>
<td>Arthralgia, n (%)</td>
<td>295 (22.6)</td>
<td>69 (5.3)</td>
</tr>
<tr>
<td>Myalgia, n (%)</td>
<td>291 (22.3)</td>
<td>84 (6.4)</td>
</tr>
<tr>
<td>Nail disorder, n (%)</td>
<td>140 (10.7)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>243 (18.6)</td>
<td>20 (1.5)</td>
</tr>
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</table>

Abbreviation: HFS, hand–foot syndrome.
Even with 70% of the patients having node-positive disease, the number of DFS events was much lower than expected, as has been observed in a number of adjuvant breast cancer trials (27–30). This low event rate substantially decreased the power of the study to show superiority of the AC—XT arm. In the subgroup of ER-positive/HER2-negative cancers, only 2% and 6% of patients whose cancers expressed Ki-67 < 10% or <20% had a DFS event at 7 years, respectively. Although patients with indolent ER-positive breast cancer may benefit long term from adjuvant therapies, our data show that their recurrence risk in the context of adjuvant endocrine therapy is exceptionally low during the first 5 years, even if they have node-positive disease. Such low recurrence rates may be related to the fact that all of the patients received chemotherapy. The ongoing TAILORx, RxPONDER, and MINDACT trials are using the 21-gene recurrence score and the 70-gene prognostic profile to confirm or refute the hypothesis that adjuvant chemotherapy does not improve the outcome of patients with slowly proliferating tumors and to thereby identify patients who may be spared treatment with chemotherapy. The very low event rate in patients with ER-positive, low Ki-67 cancers, suggests that these patients should not be enrolled in adjuvant trials that assess 5-year DFS rates, regardless of the intervention that is being evaluated. Indeed, recent adjuvant breast cancer trials such as S1207 are restricting eligibility in patients with 1 to 3 positive lymph nodes to those whose cancers have high 21-gene recurrence scores. While local Ki-67 testing is subject to inter-laboratory variability, central Ki-67 testing could be used to identify the patient population that has a very low 5-year DFS rate. In addition, given the long natural history of some types of breast cancer, expectations regarding the required length of follow-up to assess 10-year DFS rates, and the associated costs, should be incorporated into trial designs at the outset.

Disclosure of Potential Conflicts of Interest

H. Koeppen has ownership interest (including patents) in Roche. No potential conflicts of interest were disclosed by the other authors.

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