original article

Inclusion of taxanes, particularly weekly paclitaxel, in preoperative chemotherapy improves pathologic complete response rate in estrogen receptor-positive breast cancers

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Background: We examined if inclusion of a taxane and more prolonged preoperative chemotherapy improves pathologic complete response (pCR) rate in estrogen receptor (ER)-positive breast cancer compared with three to four courses of 5-fluorouracil, doxorubicin, cyclophosphamide (FAC).

Patients and methods: Pooled analysis of results from seven consecutive neo-adjuvant chemotherapy trials including 1079 patients was carried out. These studies were conducted at MD Anderson Cancer Center from 1974 to 2001. Four hundred and twenty-six (39.5%) patients received taxane-based neo-adjuvant therapy. pCR rates and survival times were analyzed as a function of chemotherapy regimen and ER status. Multivariate logistic and Cox regression analysis were carried out to identify variables associated with pCR and survival.

Results: Patients with ER-negative cancer had higher overall pCR rate than patients with ER-positive tumors (20.1% versus 4.9%, \( P < 0.001 \)). In ER-negative patients, the pCR rates were 29% and 15% with and without a taxane (\( P < 0.001 \)). In ER-positive patients, the pCR rates were 8.8% and 2.0% with and without a taxane (\( P < 0.001 \)). In multivariate analysis, clinical tumor size (\( P < 0.001 \)), ER-negative status (\( P < 0.001 \)) and inclusion of a taxane (\( P = 0.01 \)) were independently associated with pCR. For patients with pCR, survival was similar regardless of ER status or the type of regimen that induced pCR.

Conclusion: pCR rates increased for patients with both ER-positive and ER-negative tumors as regimens started to include a taxane and became longer. This indicates that a subset of patients with ER-positive breast cancer benefits from more aggressive chemotherapy, similarly to patients with ER-negative tumors.

Key words: breast cancer, estrogen receptor, neo-adjuvant, pCR, taxanes

introduction

The meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group indicated greater benefit from adjuvant chemotherapy for estrogen receptor (ER)-poor breast cancer compared with ER-rich disease [1]. For women <50 years of age, the 5-year absolute reductions in recurrence due to polychemotherapy were 13.2% and 7.6% in ER-poor and ER-rich cancers, respectively. In the older than 50-year age group, the absolute gains were smaller: 9.6% for ER-poor and 4.9% for ER-positive tumors, but remained significant (\( P < 0.00001 \)) in both groups compared with no chemotherapy.

A recent retrospective pooled analysis of three North American adjuvant clinical trials conducted by the Cancer and Leukemia Group B (8541, 9344, 9741) and the US Intergroup including >6000 patients also demonstrated that hazard reduction was twice as high in ER-negative than in ER-positive breast cancer, regardless of the treatment regimens under study [2]. The average hazard reductions for disease-free survival (DFS) were 36%, 25% and 23% for patients with ER-negative breast cancer compared with 14%, 12% and 10% for patients with ER-positive tumors in each of the three trials. These improvements in DFS, however, reached statistical significance only in the ER-negative group. These observations indicate that the majority of patients with ER-positive tumors may not benefit from adjuvant chemotherapy when appropriate adjuvant endocrine treatment is given.
Results from preoperative chemotherapy trials in stage II–III disease directly confirm that ER-negative breast cancers are more sensitive to cytotoxic therapy. Pathologic complete response (pCR) rates are consistently higher in ER-negative cancers compared with ER-positive tumors \[3, 4\]. The goal of the current study was to examine separately for ER-negative and ER-positive breast cancers how pCR rates changed over time as the preoperative regimens evolved into longer and more complex taxane-containing regimens. We also examined the prognostic value of pCR induced by the different regimens in ER-positive and ER-negative tumors.

**patients and methods**

**patient population**

This study is a meta-analysis of seven consecutively conducted Institutional Review Board-approved preoperative chemotherapy trials conducted at the University of Texas MD Anderson Cancer Center (Houston, TX) from 1974 to 2001. Clinical information was prospectively collected into a clinical trial database and updated periodically. The last update of the data with follow-up information was in December 2005. For this analysis, the final study population consisted of 1079 patients after exclusion of 185 patients with unknown ER status and 74 patients with unknown pathologic response. All patients were assigned clinical stage according to the tumor–node–metastasis classification \[5\]. The clinical stages at diagnosis were 1.7% stage I, 41.4% stage II, 23.1% stage IIIA and 33.5% stage IIIB. Patient characteristics are presented in Table 1.

**treatment**

From 1974 to 1985, the advanced primary breast cancer treatment protocol consisted of three preoperative courses of 5-fluorouracil (SP Pharmaceuticals, Albuquerque, NM, USA) (5-FU) 500 mg/m² given intravenously (i.v.) on days 1 and 4 or days 1 and 8, doxorubicin (Bedford Laboratories, Bedford, OH, USA) 50 mg/m² given as an i.v. bolus or as...
on day 1, 60–75 mg/m² of doxorubicin as a 48- to 72-h continuous i.v.
vincristine (Gensia Sicor Pharmaceuticals, Inc., Irvine, CA, USA) given i.v.
on day 1, 60–75 mg/m² of doxorubicin as a 48- to 72-h continuous i.v.
infusion, 600–750 mg/m² of cyclophosphamide given i.v. on day 1 and
40 mg of prednisone (Watson Laboratories, Corona, CA, USA) administered
orally during the first five days of each 21-day cycle (VACP) [7]. In protocol
89-007, (1989–1991), patients received four courses of preoperative FAC.
In protocol 91-015 (1991–1997), patients were randomized to four to six cycles
of standard dose preoperative FAC versus dose-escalated FAC (5-FU
600 mg/m² given on days 1 and 4, doxorubicin 60 mg/m² and
cyclophosphamide 1 gm/m² with granulocyte colony-stimulating factor
support 5 µg/kg/day) given every 2 weeks [8]. In protocol 94-002 (1994–
1998) patients were randomized to receive either four courses of FAC or four
courses of single-agent paclitaxel (Taxol, Bristol-Myers Squibb Co.,
Princeton, NJ, USA) 250 mg/m² as 24-h continuous infusion paclitaxel
therapy and all patients received four additional courses of FAC
postoperatively [9]. In protocol 97-099 (1997–1999) patients received four
courses of preoperative doxorubicin and docetaxel (Taxotere, Sanofi-
Aventis, Bridgewater, NJ, USA) 60 mg/m² each [10]. In the latest protocol,
98-240 (1998–1999) patients were randomized to weekly paclitaxel 80 or
150–175 mg/m² for 12 courses versus 250 mg/m² paclitaxel every 3 weeks
for four cycles followed by four courses of FAC, all given preoperatively [11].
Postmenopausal women with ER-positive patients received 5 years of
endocrine therapy that was started after completion of all chemotherapy.
After September 1995, adjuvant tamoxifen was also recommended to all
premenopausal women with ER-positive disease.
Patients who were considered candidates for breast conservation therapy
(BCT) were offered segmental mastectomy or lumpectomy with axillary
lymph node dissection or more recently, with sentinel lymph node biopsy.
Patients who were considered inappropriate for BCT by their surgeon or did
not desire BCT underwent modified radical mastectomy. If the surgical
margins were involved with tumor or were close (<2 mm), repeat resection
was carried out to ensure clear margins. Six hundred and fourteen (56.9%)
patients had modified radical mastectomy, 449 (41.6%) had breast-
conserving surgery and 12 (1.1%) had no surgery due to refusal or
inoperable disease. Loco-regional therapy was unknown in four (0.4%). All
patients treated with BCT received whole-breast irradiation. For patients
treated with mastectomy, chest wall and regional nodal iradation,
including the supraclavicular fossa, was carried out if the patient presented
with clinical stage III disease or there were four or more positive lymph
nodes or 24 cm residual invasive cancer detected after preoperative
chemotherapy.
After completion of locoregional therapy, patients were evaluated at 4-
month intervals during the initial 2 years and at 6-month intervals
for the next 3 years as specified in the treatment protocols. After 3 years,
patients were evaluated at yearly intervals with physical examination, laboratory study parameters (including liver chemistries), mammogram and chest radiograph.

pathologic assessment
Diagnosis of invasive cancer was established with core needle or incisional
biopsy of the tumor or fine needle aspiration of the axillary lymph node.
Tumor grade was defined according to the modified Black’s nuclear grading
system. ER status was considered positive if >10% of the neoplastic cells
showed nuclear staining on immunohistochemistry or if >10 fmol/mg
ER was detected by ligand-binding assay [12]. Pathologic response was
determined by microscopic examination of the excised tumor and nodes
after completion of chemotherapy. Grossly visible residual cancer was
measured and representative sections of the cross-sectional area were
submitted for histopathologic study. When there was not grossly visible
residual cancer, the slices of the specimen were radiographed and all areas of
radiologically and/or architecturally abnormal tissue were entirely submitted
for histopathologic study. pCR was defined as no invasive cancer in the
breast or lymph nodes. Residual ductal carcinoma in situ in the absence
of invasive cancer was also considered to be pCR.

statistical methods
Baseline clinical characteristics, including histopathologic features and the
type of preoperative regimen, were examined as variables for association
with pCR. Predictive factors of pCR were determined in univariate analysis
using Chi-square test or Fisher’s exact test. Multivariate logistic regression
model was used to determine the independent significance of each variable.
Odds ratio (OR), 95% confidence intervals (CI) and P values were estimated.
Separate analysis was carried out for all patients and for patients with
ER-negative and ER-positive disease. Treatments that included paclitaxel
or docetaxel together with an anthracycline were considered together as
‘taxane-containing’ regimens. All survival statistics were measured from
the date of diagnosis. The actuarial rates of survival and recurrences were
calculated according to the Kaplan–Meier method and comparisons were
made using the log-rank test. A multivariate analysis using the Cox
proportional hazards regression model was used to determine predictive
factors of survival and logistic regression for pathologic response.
All tests were two-tailed and a P value <0.05 was considered significant.
All statistical analyses were carried out with SPSS® version 12.0 software.

results
pathologic response
Of the 1079 patients, 131 (12.1%) had pCR. Clinical and
pathological characteristics of patients are presented in Table 1.
In univariate analysis, smaller clinical tumor size at diagnosis
(P < 0.001), invasive ductal histology (compared with ILC)
(P = 0.02), high Black’s modified nuclear grade (P < 0.001),
ER-negative status (P < 0.001) and inclusion of a taxane (P < 0.001)
were found to be significantly associated with higher rate of pCR.
In multivariate analysis of the entire population, clinical tumor
size (OR 0.6, 95% CI 0.5–0.7, P < 0.001), ER-negative status (OR
6.9, 95% CI 4.3–11.1, P < 0.001) and inclusion of a taxane (OR
1.8, 95% CI 1.1–2.9, P = 0.01) were independently associated
with pCR. Because the earlier neo-adjuvant studies included
more locally advanced patients and the more recent studies
included many patients with stage II (and some stage I) breast
cancers, we also examined the impact of this stage shift on pCR
rate. We categorized year of surgery into quarters with roughly
1999, 2000–2002). The proportion of stage III cancers decreased
over time in each quarter but the pCR rate increased within each
quarter over time. Thus, the decrease in the proportion of stage
III patients included in the studies does not fully account for the
increase in pCR over time. A logistic regression analysis
estimated that the odds of pCR increase 9% (relative not absolute
increase) per year after adjusting for stage (P = 0.011).
The pCR rate was 21.8% in the sequential paclitaxel plus FAC
treatment group (n = 247) that also received the longest
preoperative therapy, 6-months in total. The pCR rate was
16.1% in the group who received four courses of concurrent
doxorubicin and docetaxel (n = 87) and it was 6.5% in the
paclitaxel-alone group \((n = 92)\) who received four courses of preoperative paclitaxel (q3-week schedule). The pCR rate in the anthracycline-alone group \((n = 653)\) who received three to four courses of FAC or VACP was 8.7%. The increased pCR rate seen with taxane plus anthracycline regimens compared with anthracycline alone was statistically significant \((P < 0.001)\).

When the pCR rates were examined separately for ER-positive and ER-negative patients, the pCR rates were higher in ER-negative patients for each chemotherapy regimen (20.1% versus 4.9%, \(P < 0.001\)) (Table 2). pCR rates, however, increased for patients with both ER-negative and ER-positive tumors as the regimens started to include a taxane and became longer. For the patients with ER-negative breast cancer, preoperative regimens that included a taxane and anthracycline had an overall pCR rate of 29% compared with 15% with anthracycline therapy alone \((P < 0.001)\). For the patients with ER-positive tumors, preoperative regimens that included a taxane (plus anthracycline) had an overall pCR rate of 8.8% compared with 2% with anthracycline therapy alone \((P < 0.001)\). This indicates that a subset of patients with ER-positive tumors benefit from more aggressive chemotherapy proportionally similarly to patients with ER-negative tumors but the absolute benefit is smaller because the chemotherapy-sensitive subpopulation is smaller among ER-positive than in ER-negative cancers.

### overall and DFS

The median overall survival (OS) for the 1076 patients with 420 events was 13 years (95% CI 11–21). Considering all patients, the overall 10-year DFS was slightly better for the ER-positive group compared with patients with ER-negative breast cancer (60% versus 56.8%, \(P = 0.004\)). Patients who achieved pCR had a better 5- and 10-year DFS than patients with residual disease. The 10-year DFS were 86% versus 55% \((P < 0.001)\), respectively. A Cox proportional hazards model for OS, including pCR, age, ER status, menopausal status, T-stage, nodal status, histology, grade, progesterone receptor status and chemotherapy type, yielded an hazard ratio (HR) for pCR = 0.3 (0.2, 0.5) with \(P < 0.0001\). Other significant variables were age, ER status, T-stage, nodal status, grade and type of chemotherapy. There were no significant interactions between pCR and any of the other variables indicating that it was independent of these other variables. Only 862 patients are included in the model due to missing data.

Thirty-three percent of all patients experienced local or distant recurrence at a median follow-up of 85.3 months (range 2–345 months). Computing freedom from recurrence from date of surgery, with 349 events in 1079 patients, 88% was recurrence free at 1 year, 75% at 3 years, 70% at 5 years, 65% at 10 years and 62% at 20 years. The HR for recurrence reached a peak just after 1 year and then fell sharply to year 4. After year 4, the hazard function fell more gradually approaching zero at 20 years. Among women who achieved pCR, the freedom from recurrence was 98% at 1 year, 93% at 3 years, 92% at 5 years and 92% at 10 years. In Cox multiple regression analysis, larger clinical tumor size at diagnosis (hazard ratio 1.3, \(P < 0.001\)), ER-negative status (hazard ratio 1.4, \(P < 0.01\)), were unfavorable predictive factors of DFS. Achievement of pCR (hazard ratio 0.2, \(P < 0.001\)) and inclusion of a taxane (hazard ratio 0.7, \(P < 0.001\)) were the favorable predictors of DFS.

| Table 2. pCR rates as function of ER status and chemotherapy \(^\text{a}\) regimen |
|-----------------|-------------|-------------|--------------|
|                 | ER negative | ER positive | \(P\) value |
| VACP 4× \((n = 138)\) | 6 (9%)      | 0 (0)       | 0.01        |
| Paclitaxel 4× \((n = 92)\) | 3 (9.4%)    | 3 (5%)      | 0.42        |
| FAC 3–4× \((n = 515)\) | 45 (16.8%)  | 6 (2.4%)    | <0.001      |
| Docetaxel + doxorubicin 4× \((n = 87)\) | 11 (20.8%) | 3 (8.8%)    | 0.13        |
| Paclitaxel q3-week 4× + FAC 4× \((n = 123)\) | 15 (29.4%) | 4 (5.6%)    | <0.001      |
| Paclitaxel q1week 12× + FAC 4× \((n = 124)\) | 23 (54.8%) | 12 (14.6%)  | <0.001      |
| Total \((n = 1079)\) | 103 (20.1%) | 28 (4.1%)   | <0.001      |

\(^{a}\)For details of chemotherapy regimens including doses of drugs see patients and methods section.

pCR, pathologic complete response; ER, estrogen receptor; FAC, 5-fluorouracil, doxorubicin, cyclophosphamide.

There was no statistically significant difference in OS and DFS within the pCR group by treatment regimen. In particular, there was no statistically significant difference between the survival of patients who achieved pCR with anthracycline-only therapy compared with those with anthracycline and taxanes (Figure 1). The OS rates were 88.7% and 94.5% at 5 years, respectively \((P = 0.46)\), and the 5-year DFS rates were 91.8% and 98.2% at 5 years, respectively \((P = 0.27)\). pCR heralded good OS and DFS regardless of ER status and the type of regimen that induced this favorable response. The 5-year OS was 96% for ER-negative patients and it was 92% for ER-positive patients with pCR, which were not statistically different \((P = 0.99)\). The 5-year DFS were 88% and 93%, respectively \((P = 0.72)\). Figure 2 shows OS of patients who achieved pCR by ER status and by treatment type (on this figure, patients who achieved pCR with single-agent paclitaxel are included among the taxane group).

### discussion

pCR to preoperative chemotherapy is a direct measure of extreme chemotherapy sensitivity. All studies that examined the correlation between pathologic response and long-term outcome showed a strong correlation between pCR and prolonged DFS and OS [3, 13–17]. It may be argued that pCR identifies a subset of patients who had good prognosis to start with and therefore the prolonged DFS and OS is not due to their favorable response to therapy but reflect the indolent nature of their disease. This is unlikely because the clinical and pathological features that are associated with higher probability of pCR, including ER negativity, high grade, high proliferation rate and high OncotypeDx recurrence score are all predictors of poor prognosis in the absence of chemotherapy [18–21]. It is more likely that patients who achieve pCR do well because they benefited from chemotherapy through eradication of micrometastatic disease that originated from an extremely chemotherapy-sensitive primary tumor. pCR, however, remains an imperfect surrogate of benefit because recurrences continue
to occur in this group of patients [12]. Also, to what extent
patients who achieve less than pCR benefited from
chemotherapy, in terms of improved survival, is unknown.
It is impossible to determine this from retrospective analysis
of single-arm clinical trials.

In this paper, we examined pCR rates in seven consecutive
neo-adjuvant chemotherapy trials conducted at a single
institution over two decades. pCR rates increased with more
recent regimens. This trend was observed for all clinical stages
and for both ER-negative and ER-positive cancers. ER-negative
tumors consistently showed higher pCR rates than ER-positive
cancers. pCR rates, however, can be as high as 14.6% in ER-
positive patients included in the most recent study treated with
12 courses of weekly paclitaxel followed by four courses of FAC
chemotherapy. The improved pCR rates among ER-positive
patients are primarily due to the optimized weekly schedule

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**Figure 1.** (A) Overall survival for all patients \( (n = 1079) \) as function of pathological response. (B) Overall survival of patients with pathologic complete response \( (pCR) \) by treatment regimen.

**Figure 2.** (A) Overall survival of estrogen receptor \( (ER) \)-negative patients who achieved pathologic complete response by treatment regimen. (B) Overall survival of ER-positive patients who achieved pathologic complete response by treatment regimen.
of paclitaxel administration. All taxane-including regimens, however, produced higher pCR rates compared with three to four cycles of anthracycline-based regimens. There are important caveats of these findings. We examined pCR rates in sequential neo-adjuvant clinical trials and the patient population included in these trials has changed over time. Earlier trials with anthracycline alone tended to include more patients with locally advanced breast cancer than the more recent taxane-including studies. Multivariable analysis, however, indicated inclusion of a taxane, which also meant more prolonged chemotherapy (except for patients who received four courses of doxorubicin/docetaxel) was an independent predictor of pCR even after adjustment for tumor size. Also, ER was measured by ligand-binding assay until about the early 1990s and by IHC since then. While the two techniques are similar, the results are not completely overlapping. It is unlikely that the change in ER assessment has major confounding effect in our observations. It is also possible that the delivery of chemotherapy has improved over time. Patients accrued more recently may have received higher dose density and greater cumulative dose due to less dose delays or less frequent discontinuation of therapy (due to availability of colony-stimulating factors). These and other unexpected covariates may have influenced our results. Our observations, however, corroborate results from a larger randomized clinical trial, NSABP-B27. This study also reported improved pCR rates in both ER-negative and ER-positive patients after inclusion of four courses of docetaxel with four courses of doxorubicin/cyclophosphamide (AC) compared with AC alone [22].

pCR predicts for good survival in patients with both ER-negative and ER-positive tumors; therefore, the subset of patients with ER-positive tumors who achieved pCR probably benefited substantially from their chemotherapy. An important finding of our study is that the prognostic value of pCR was similar regardless of the type of chemotherapy that induced it and was also independent of ER status. Once pCR was achieved, survival was equally good for those who achieved this favorable response with single-agent paclitaxel or four courses of anthracycline therapy alone or with more prolonged sequential anthracycline and taxane therapy. This observation is also consistent with results from the NSABP-B27 study; patients with pCR did equally well regardless whether their treatment included docetaxel or not. On the basis of these results, we consider pCR the best currently available early surrogate of benefit from chemotherapy in both ER-positive and ER-negative breast cancers. A small subset of ER-positive cancers is highly chemotherapy sensitive and more aggressive treatment with inclusion of a taxane, particularly weekly paclitaxel, can improve pCR rates among these patients. For future clinical trials, it will be critically important to prospectively identify the subset of ER-positive patients who are sensitive to cytotoxic therapy and therefore benefit from adjuvant or neo-adjuvant chemotherapy.

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references


