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REVIEW ARTICLE

Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27

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ABSTRACT

Purpose

National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18 was designed to determine whether four cycles of doxorubicin and cyclophosphamide (AC) administered preoperatively improved breast cancer disease-free survival (DFS) and overall survival (OS) compared with AC administered postoperatively. Protocol B-27 was designed to determine the effect of adding docetaxel (T) to preoperative AC on tumor response rates, DFS, and OS.

Patients and Methods

Analyses were limited to eligible patients. In B-18, 751 patients were assigned to receive preoperative AC, and 742 patients were assigned to receive postoperative AC. In B-27, 784 patients were assigned to receive preoperative AC followed by surgery, 783 patients were assigned to AC followed by T and surgery, and 777 patients were assigned to AC followed by surgery and then T.

Results

Results from B-18 show no statistically significant differences in DFS and OS between the two groups. However, there were trends in favor of preoperative chemotherapy for DFS and OS in women less than 50 years old (hazard ratio [HR] = 0.85, $P = .09$ for DFS; HR = 0.81, $P = .06$ for OS). DFS conditional on being event free for 5 years also demonstrated a strong trend in favor of the preoperative group (HR = 0.81, $P = .053$). Protocol B-27 results demonstrated that the addition of T to AC did not significantly impact DFS or OS. Preoperative T added to AC significantly increased the proportion of patients having pathologic complete responses (pCRs) compared with preoperative AC alone (26% *v* 13%, respectively; $P < .0001$). In both studies, patients who achieved a pCR continue to have significantly superior DFS and OS outcomes compared with patients who did not.

Conclusion

B-18 and B-27 demonstrate that preoperative therapy is equivalent to adjuvant therapy. B-27 also showed that the addition of preoperative taxanes to AC improves response.

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INTRODUCTION

Preoperative therapy, initially used only for locally advanced breast cancer, has become more common for patients with operable disease.[1-17] This allows more individuals to undergo breast-conserving procedures and provides for observation of response to treatment. Long-term outcome significantly correlates with both clinical and pathologic tumor response rates.[9,14,17-19] We provide here an update of extended outcomes for two preoperative chemotherapy trials of the National Surgical Adjuvant Breast and Bowel Project (NSABP), Protocols B-18 and B-27.

The primary aim of Protocol B-18 was to determine whether preoperative chemotherapy with doxorubicin and cyclophosphamide (AC) would result in improved overall survival (OS) and disease-free survival (DFS) compared with postoperative adjuvant chemotherapy. Secondary aims were to evaluate the response of the primary breast tumor and involved lymph nodes to preoperative chemotherapy, to correlate the response with outcomes, and to determine whether preoperative chemotherapy increased use of breast-conserving surgery and decreased rates of ipsilateral breast tumor recurrence. We previously reported results through 9 years of follow-up.[13-15] There were no significant differences in DFS and OS between groups. We now update results through 16 years of follow-up.

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The primary objective of Protocol B-27 was to determine whether adding docetaxel (T) to preoperative AC would increase DFS and OS in patients with operable breast cancer. Clinical and pathologic responses in the breast and axillary nodal downstaging were assessed. We previously reported results through 6.5 years of follow-up[16,17] and now update results through 8.5 years of follow-up.

PATIENTS AND METHODS

Eligibility and Entry Procedures

Protocol B-18 opened in October 1988 and closed in April 1993. Patient characteristics are listed in Table 1. Of the 1,523 patients, 763 were randomly assigned to the preoperative chemotherapy group, and 760 were assigned to the postoperative chemotherapy group. Details of enrollment, eligibility, and stratification variables have been described previously.[13-15] Eligible patients for B-18 had operable, palpable breast cancer (T1-3, N0-1, M0) diagnosed by core needle biopsy or fine-needle aspirate (FNA).

NSABP Protocol B-27 was opened to accrual in December 1995 and closed in December 2000 after 2,411 patients had been randomly assigned. Patient characteristics for B-27 are listed in Table 1. Women who had primary operable breast cancer (T1c-3, N0-1, M0 or T1-3, N1, M0) diagnosed by core biopsy or FNA were eligible.

The stratification variables for both studies were age, clinical tumor size, and clinical nodal status. Because FNA results could be used to establish eligibility, hormone receptor status was not available at random assignment for these patients, so it was not used as a stratification variable. Both protocols had to be approved by the local human investigations committee or institutional review board, with assurances filed with and approved by the US Department of Health and Human Services. Patients were required to give written consent to enter the studies.

Treatment

In Protocol B-18, patients were randomly assigned to either surgery (lumpectomy and axillary lymph node dissection or modified radical mastectomy) followed by four cycles of AC chemotherapy (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) every 21 days or the same chemotherapy followed by surgery. Before random assignment, surgeons were required to disclose the intended surgical procedure (lumpectomy or mastectomy) without considering possible downstaging by chemotherapy. Patients ≥ 50 years of age received tamoxifen 10 mg orally twice a day for 5 years, starting after chemotherapy, regardless of hormone receptor status, whereas women less than 50 years of age did not receive hormonal therapy. Patients undergoing lumpectomy received whole-breast irradiation. Details of treatment have been described previously.[13-15]

In Protocol B-27, all patients were assigned to receive four cycles of AC every 21 days before surgery. Patients in groups 1 and 3 did not receive further preoperative chemotherapy, whereas patients in group 2 were assigned to receive four cycles of T preoperatively at 100 mg/m^2 every 21 days. After the completion of AC in groups 1 and 3 or AC followed by T in group 2, patients underwent surgery (either lumpectomy plus axillary node dissection or modified radical mastectomy). Patients in group 3 received four cycles of postoperative T (100 mg/m^2). In all study patients, tamoxifen (20 mg/d for 5 years)

Table 1. National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27: Patient Characteristics

Characteristic	Protocol B-18		Protocol B-27		
	Postoperative AC	Preoperative AC	Preoperative AC	Preoperative AC + T	Preoperative AC + Postoperative T
No. of patients					
Entered onto study	763	760	804	805	802
Ineligible	7	14	18	21	23
Without follow-up	7	5	2	1	2
Eligible with follow-up	751	742	784	783	777
Median time on study, months*	192	192	102	102	102
Age, years, %†‡					
≤ 49	52	51	57	56	57
50-59	26	25	30	30	30
≥ 60	22	23	14	14	13
Mean	49.7	50.4	48.5	48.5	48.1
Standard deviation	10.8	10.6	9.9	9.8	9.7
Race/ethnicity, %†					
White	81	81	74	76	75
Black	11	9	12	11	13
Other	7	8	11	10	11
Unknown	1	1	3	2	2
Clinical tumor size, cm, %†§					
≤ 2.0	27	28	15	14	14
2.1-5.0	60	59	57	58	57
≥ 5.1	13	13	29	28	29
Mean‡	3.5	3.5	4.5	4.4	4.5
Standard deviation	1.8	1.8	2.3	2.2	2.3
Clinical nodal status, %†‡					
Negative	74	74	70	70	69
Positive	26	26	30	30	31

Abbreviations: AC, doxorubicin and cyclophosphamide; T, docetaxel.
*As of December 31, 2006.
†Values are percentage of patients included in the analysis of end point results.
‡As reported by the institution at entry.
§Note that Protocol B-18 was stratified by clinical tumor size as ≤ 2.0, 2.1-5.0, or ≥ 5.1 cm, whereas Protocol B-27 was stratified as ≤ 2.0, 2.1-4.0, or ≥ 4.1 cm.

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was to be initiated on the first day of chemotherapy regardless of age or hormone receptor status. Patients undergoing lumpectomy were to receive a course of radiotherapy to the breast. Regional radiotherapy or radiotherapy to the chest wall after mastectomy was prohibited. Details of treatment have been described previously.[16,17]

Tumor Response

Before each chemotherapy treatment and before surgery, the two greatest perpendicular diameters of the tumors in the breast and axillary nodes were measured, and the products of these diameters were added as a measure of total tumor size. No clinical evidence of palpable tumor in the breast and axillary lymph nodes was defined as a clinical complete response (cCR). Reduction of the sum of the products of the tumor masses by 50% or greater was classified as a clinical partial response. An increase in the sum of the products of more than 50% or appearance of new suspicious ipsilateral axillary adenopathy was considered progressive disease. Tumors that did not meet the criteria for response or progression were classified as stable disease. Surgical specimens with no invasive cancer in the breast were considered to be a pathologic complete response (pCR).

Other End Points

The primary end points for these analyses across protocols were OS, DFS, and relapse-free interval (RFI). For each type of event, the time to the first occurrence of that event was analyzed. Analyses of OS included all deaths regardless of etiology. Events for the calculation of DFS included all local, regional, or distant recurrences; clinically inoperable disease; gross residual disease after surgery; all second cancers and contralateral breast cancers; and all deaths. Events for the calculation of RFI included the first occurrences of local, regional, and distant breast cancer recurrences; clinically inoperable disease; and gross residual disease after surgery, whereas occurrences of contralateral breast cancer, other second primary cancers, and deaths without evidence of recurrence were treated as censoring events.

Statistical Methodology

Simple log-rank tests and Cox proportional hazards models[20] were used to make formal inferences about group comparisons, and Kaplan-Meier curves[21] were used to quantify the values of OS, DFS, and RFI over time. In the Cox regression analyses, adjustments were made for age, clinical nodal status, and clinical tumor size according to the stratification schemes used in each protocol. The postoperative AC group in B-18 and the preoperative AC group in B-27 were used as the control (baseline) groups for the calculation of hazard ratios (HRs) in all of the treatment group comparisons. Analyses were also performed to determine whether significant treatment by stratification variable interactions existed with respect to the end points.[22] Site-specific failure rates were calculated by using cumulative incidence curves.[23] Cause-specific HRs for the site-specific end points in each study were obtained by adjusting for the stratification variables in that study.[24] *P* values for treatment comparisons of cumulative incidence curves were obtained by using the method proposed by Fine and Gray.[25,26] In the forest plots displaying comparisons of

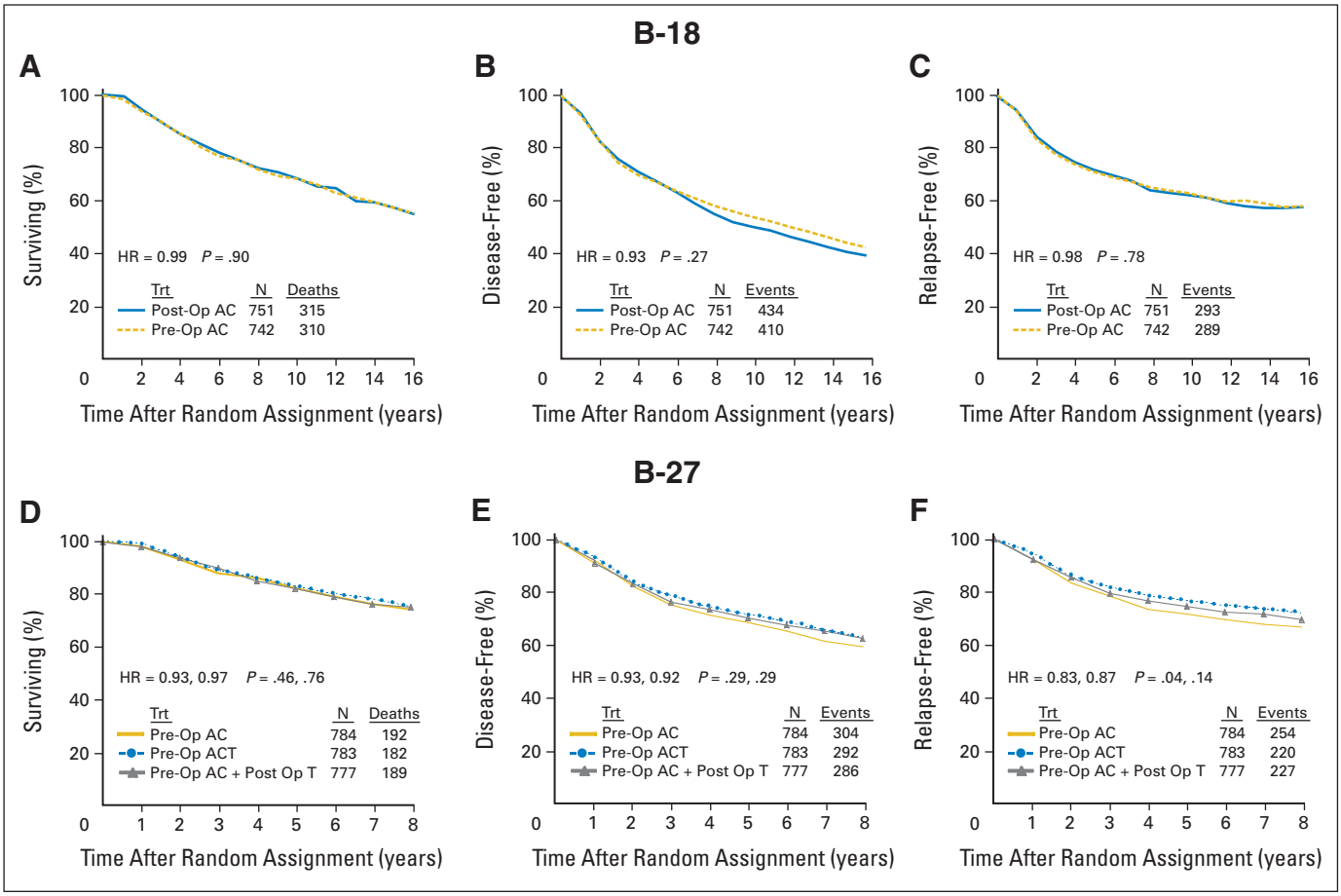

Fig 1. (A) Overall survival (OS) in National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18. (B) Disease-free survival (DFS) in NSABP Protocol B-18. (C) Relapse-free interval (RFI) in NSABP Protocol B-18. (D) OS in NSABP Protocol B-27. (E) DFS in NSABP Protocol B-27. (F) RFI in NSABP Protocol B-27. HR, hazard ratio; Post-Op, postoperative; Pre-Op, preoperative; AC, doxorubicin and cyclophosphamide; T, docetaxel.

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subsets defined by stratification variables, HRs reflect unadjusted treatment comparisons.

Analyses of end point data are based on information received at the NSABP Biostatistical Center as of December 31, 2006, at which time, 625 deaths, 844 DFS events, and 582 RFI events had been reported in eligible B-18 patients and 563 deaths, 882 DFS events, and 701 RFI events had been reported in eligible B-27 patients. The median times on study for eligible patients with follow-up information on B-18 and B-27 were 16.0 and 8.5 years, respectively.

RESULTS

Patient Characteristics

Baseline patient characteristics within each protocol are listed in Table 1. B-18 patients, compared with B-27 patients, were slightly older at entry (50.0 *v* 48.4 years, respectively; $P < .001$), had smaller tumors (average clinical tumor size, 3.5 *v* 4.5 cm, respectively; $P < .001$), and had a significantly lower frequency of clinically positive nodes (26% *v* 30%, respectively; $P = .02$). B-18 also had a larger proportion of white women than B-27 ($P < .001$).

Response

In the preoperative AC group of Protocol B-18, an objective clinical response occurred in 79% of the assessable patients, with a clinical partial response in 43% and a cCR in 36%. A pCR was documented in 13% of patients. Preoperative chemotherapy patients had a significantly increased incidence of pathologically negative axillary nodes compared with patients randomly assigned to postoperative chemotherapy (58% *v* 42%, respectively; $P < .0001$). Moreover, 68% of individuals in the preoperative group had breast-conserving surgery compared with 60% of individuals in the postoperative chemotherapy group ($P = .001$).

In Protocol B-27, 86% of the patients in the two groups assigned to receive preoperative AC only (groups 1 and 3) achieved a clinical response compared with 91% of patients in the preoperative AC and T group ($P < .001$). The cCR rate was increased from 40% to 63% with the addition of four cycles of T ($P < .001$). The pCR rate was increased from 13% in groups 1 and 3 to 26% in group 2 ($P < .001$).

Survival

In Protocol B-18, there continue to be no statistically significant differences in survival between the two groups (HR = 0.99; 95% CI, 0.85 to 1.16; $P = .90$; Fig 1A). The 5-, 8-, and 16-year survival estimates were 81%, 72%, and 55%, respectively, in the postoperative group and 80%, 72%, and 55%, respectively, in the preoperative group. OS conditional on being alive at 5 years was not significantly different between the two groups (HR = 0.94; $P = .56$; data not shown).

In Protocol B-27, there continue to be no statistically significant differences in OS according to treatment (*P* across all three arms = .76; Fig 1D). The 5- and 8-year survival estimates were 82% and 74% in group 1, 83% and 75% in group 2, and 82% and 75% in group 3, respectively.

DFS

In Protocol B-18, there have been 434 events in the postoperative group and 410 events in the preoperative group, with no significant difference in DFS between the two groups (HR = 0.93; 95% CI, 0.81 to 1.06; $P = .27$; Fig 1B). The 5-, 8-, and 16-year DFS estimates were 67%, 55%, and 39% in the postoperative group and 67%, 58%, and 42% in the preoperative group, respectively. DFS conditional on being event free for 5 years demonstrated a trend for benefit in favor of the preoperative group (HR = 0.81; 95% CI, 0.66 to 1.00; $P = .053$; Fig 2).

In Protocol B-27, 304, 292, and 286 events were reported in groups 1, 2, and 3, respectively. There continue to be no statistically significant differences according to treatment for DFS (group 2 *v* group 1: HR = 0.92; 95% CI, 0.78 to 1.08; $P = .29$; group 3 *v* group 1: HR = 0.92; 95% CI, 0.78 to 1.08; $P = .29$; Fig 1E). The 5- and 8-year DFS estimates were 68% and 59% in group 1, 71% and 62% in group 2, and 70% and 62% in group 3, respectively.

RFI

There was no significant difference in RFI between the two treatment groups in B-18 (HR = 0.98; 95% CI, 0.83 to 1.15; $P = .78$; Fig 1C). In B-27, both groups assigned to receive T seemed to do better than the group treated with AC alone (group 2 *v* group 1: HR = 0.83; 95% CI, 0.69 to 0.99; $P = .04$; group 3 *v* group 1: HR = 0.87; 95% CI, 0.73 to 1.04; $P = .14$; Fig 1F). The 5- and 8-year RFI estimates were 71% and 66% in group 1, 76% and 71% in group 2, and 74% and 69% in group 3, respectively.

First Reported Sites of Treatment Failure

There continue to be no statistically significant differences in the rates of treatment failure at any specific site in B-18 (Table 2). There was a trend toward a higher rate of ipsilateral breast tumor recurrence with preoperative chemotherapy versus postoperative chemotherapy (13% of 506 patients *v* 10% of 450 patients, respectively); however, this difference was not statistically significant ($P = .21$). The cumulative incidences of all local recurrences as well as distant recurrences were not significantly different between the two groups ($P = .08$ and $P = .22$, respectively). In B-27, there continued to be a significant decrease in the cumulative incidence of all local recurrences as first events in patients assigned to receive T (groups 2 and 3) compared with patients who did not receive T (group 1; HR = 0.67; $P = .02$). However, there were no other significant differences in the cumulative incidence of recurrences at any other sites of first failure (Table 3).

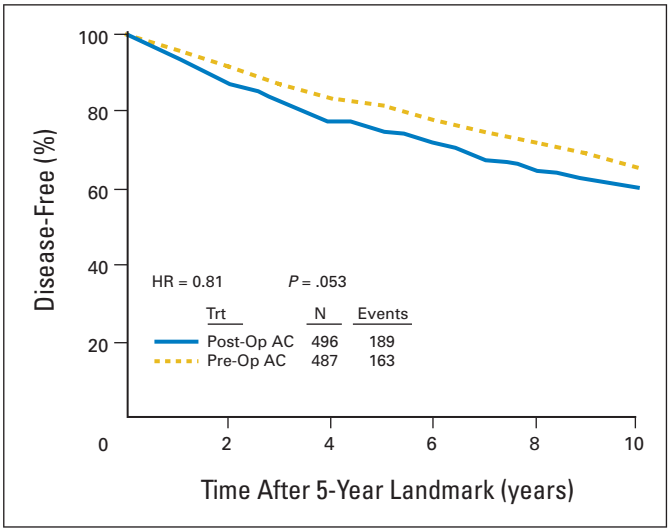

Fig 2. National Surgical Adjuvant Breast and Bowel Project Protocol B-18: disease-free survival conditional on being event free for 5 years. HR, hazard ratio; Post-Op, postoperative; Pre-Op, preoperative; AC, doxorubicin and cyclophosphamide.

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Table 2. National Surgical Adjuvant Breast and Bowel Project Protocol B-18: First Reported Site of Treatment Failure in Eligible Patients

Treatment Failure	Postoperative AC		Preoperative AC		Total	
	No. of Patients	%	No. of Patients	%	No. of Patents	%
Inoperable						
Clinically inoperable	0	0	1	< 1	1	< 1
Gross residual disease	11	1	8	1	19	1
IBTR only*	46	10	66	13	112	12
Local recurrence, except IBTR	23	3	24	3	47	3
Regional recurrence	35	5	29	4	64	4
Distant metastasis, except opposite breast	178	24	161	22	339	23
Second cancer, except opposite breast	54	7	48	6	102	7
Opposite breast, metastasis or second cancer	48	6	38	5	86	6
Dead, NED	39	5	35	5	74	5
Total first events	434	58	410	55	844	57
Alive, event free	317	42	332	45	649	43
Total patients	751	100	742	100	1493	100

Abbreviations: AC, doxorubicin and cyclophosphamide; IBTR, ipsilateral breast tumor recurrence; NED, no evidence of disease.
*Percentage for IBTR is based on the number of patients who received lumpectomy.

Treatment-by-Covariate Interactions and Subset Analyses

In Protocol B-18, there was a significant treatment-age interaction for OS ($P = .01$) and nearly significant treatment-by-age interactions for DFS and RFI ($P = .14$ and $P = .06$, respectively). Specifically, there was a trend in favor of preoperative chemotherapy compared with postoperative therapy for OS and DFS in women younger than 50 years old (OS: HR = 0.81, $P = .06$; DFS: HR = 0.85, $P = .09$). At 16 years of follow-up, in women less than 50 years old, OS was 55% in the postoperative chemotherapy group compared with 61% in the preoperative chemotherapy group, and DFS was 38% *v* 44%, respectively. Conversely, in women ≥ 50 years at entry, there was a trend in favor of postoperative chemotherapy for OS (HR = 1.23, $P = .07$). At 16 years of follow-up, the OS in the postoperative and preoperative chemotherapy groups was 55% and 50%, respectively. DFS was not statistically different between treatment groups for women more than 50 years of age at entry (HR = 1.03, $P = .76$). No other significant treatment-by-covariate interactions were found in B-18 (Fig 3). In Protocol B-27, no significant heterogeneity of treatment effect was detected across age categories or the other stratification variables.

Association Between Pathologic Response and Outcome

In B-18, individuals who achieved a pCR continue to have superior DFS and OS outcomes compared with patients who did not achieve a pCR (DFS HR = 0.47, $P < .0001$; OS HR = 0.32, $P < .0001$; Fig 4A). Through 8 years of follow-up on

Table 3. National Surgical Adjuvant Breast and Bowel Project Protocol B-27: First Reported Site of Treatment Failure in Eligible Patients

Treatment Failure	Preoperative AC		Preoperative AC + Preoperative T		Preoperative AC + Postoperative T		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Inoperable								
Clinically inoperable	0	0	5	1	0	0	5	< 1
Gross residual disease	17	2	12	2	21	3	50	2
IBTR only*	33	7	28	6	25	5	86	6
Local recurrence, except IBTR	35	4	19	2	23	3	77	3
Regional recurrence	20	3	14	2	20	3	54	2
Distant metastasis, except opposite breast	149	19	142	18	138	18	429	18
Opposite breast, metastasis or second cancer	13	2	19	2	25	3	57	2
Second cancer except opposite breast	21	3	36	5	21	3	78	3
Dead, NED	16	2	17	2	13	2	46	2
Total first events	304	39	292	37	286	37	882	38
Alive, event free	480	61	491	63	491	63	1462	62
Total patients	784	100	783	100	777	100	2344	100

Abbreviations: AC, doxorubicin and cyclophosphamide; T, docetaxel; IBTR, ipsilateral breast tumor recurrence; NED, no evidence of disease.
*Percentage for IBTR is based on the number of patients who received lumpectomy.

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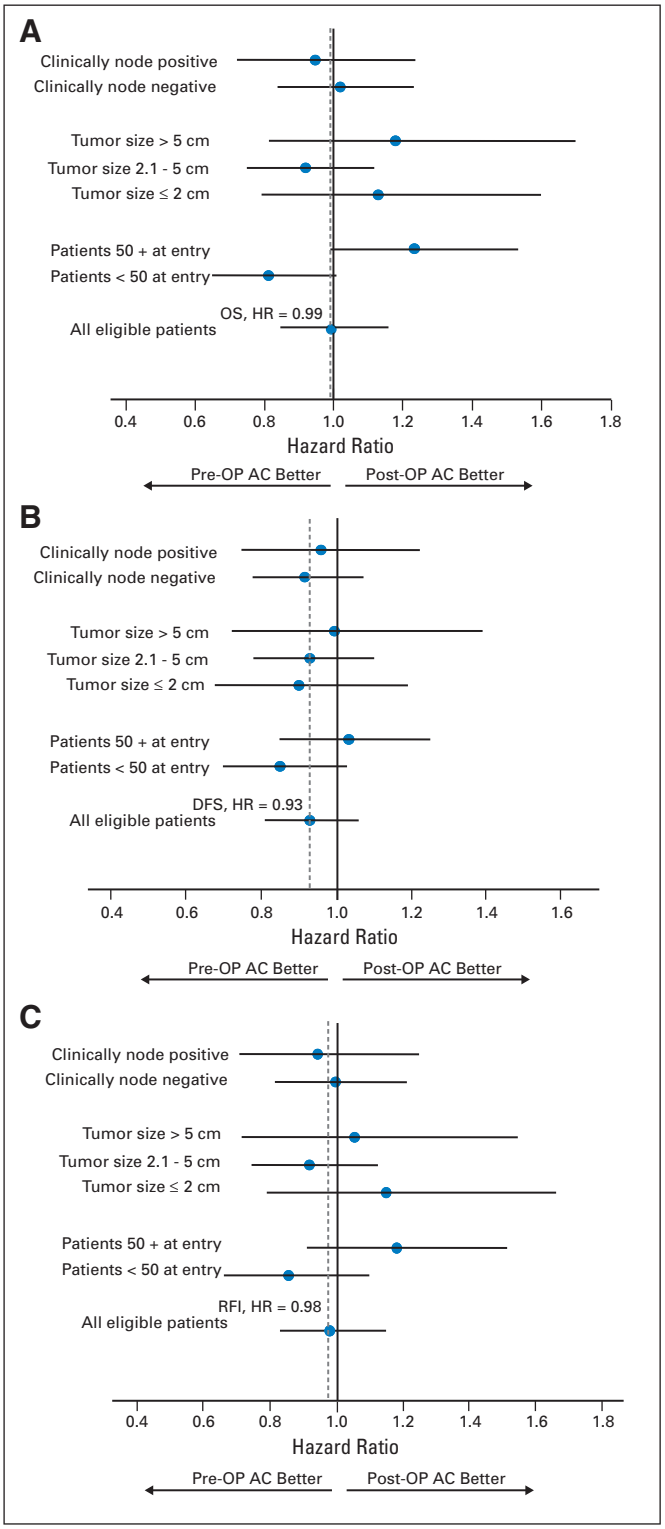

Fig 3. Forest plots for National Surgical Adjuvant Breast and Bowel Project Protocol B-18 for overall survival (OS), disease-free survival (DFS), and recurrence-free interval (RFI) by clinical node status, clinical tumor size, and age. HR, hazard ratio; Post-Op, postoperative; Pre-Op, preoperative; AC, doxorubicin and cyclophosphamide.

Protocol B-27, pCR remained a highly significant predictor of improved DFS (HR = 0.49, $P < .0001$) and OS (HR = 0.36, $P < .0001$; Fig 4B). Separate multivariate analyses indicated that

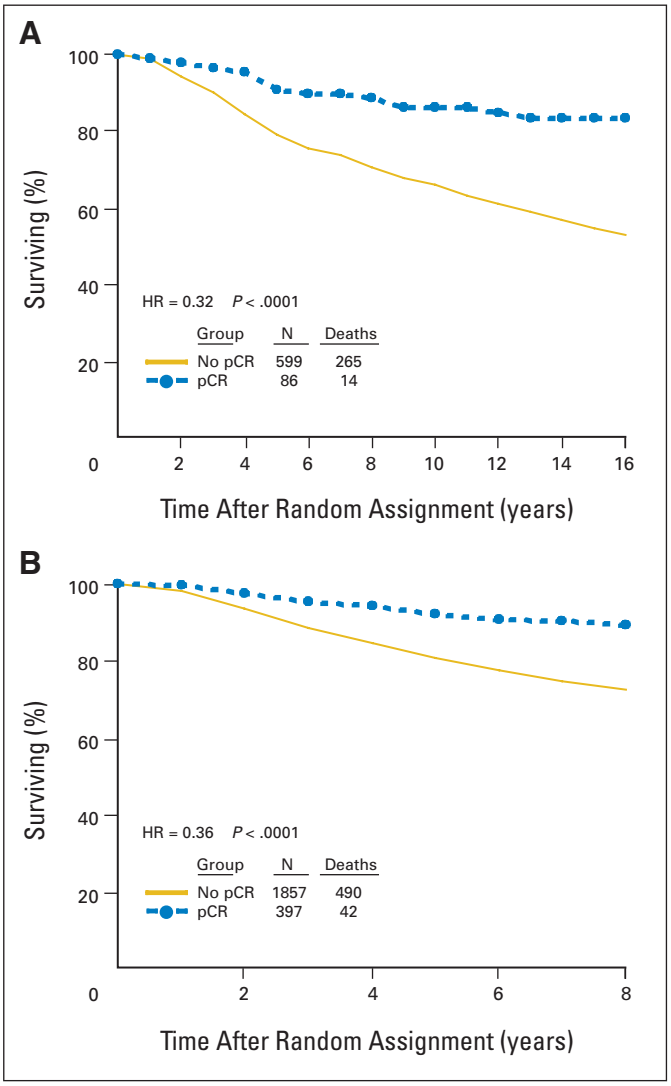

Fig 4. Survival by pathologic complete response (pCR) status in patients who received preoperative doxorubicin and cyclophosphamide. (A) National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18: group 2 patients. (B) NSABP Protocol B-27: all patients. HR, hazard ratio.

post-treatment pathologic nodal status was also a strong predictor of OS and DFS in both B-18 and B-27 ($P < .0001$ for both end points in both protocols).

DISCUSSION

Although there were no significant differences in OS or DFS overall in Protocol B-18, women less than 50 years of age seemed to benefit from preoperative versus postoperative chemotherapy. In contrast, women ≥ 50 years old had better outcomes with postoperative chemotherapy. These results were initially presented at 9 years on study[15] and persist after a median of 16 years on study. The overview analyses from the Early Breast Cancer Trialists' Collaborative Group[27] indicate that the effects of chemotherapy are most apparent in younger women. It is possible that the benefit of preoperative chemotherapy relative to postoperative chemotherapy could be age dependent as well. In addition, younger women are more likely to have estrogen

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receptor (ER) –negative tumors,[28] and International Breast Cancer Study Group data suggest there may be a preferential benefit to early initiation of adjuvant chemotherapy in premenopausal women with ER-negative tumors.[29] Tumors that are ER negative also tend to have a higher pathologic response rate to chemotherapy than ER-positive tumors.[16,30-32] In the adjuvant setting, data suggest that the absolute benefits from chemotherapy are greater with ER-negative tumors compared with ER-positive tumors.[33] Additionally, analyses from the Early Breast Cancer Trialists' Collaborative Group demonstrated that chemotherapy versus no chemotherapy and anthracycline versus nonanthracycline chemotherapy had greater absolute benefit in the ER-negative and ER-poor subsets.[34] These explanations are speculative but may explain why younger women seemed to have a greater benefit from preoperative chemotherapy. Because of the limitations on the availability of hormone receptors from the B-18 study, data are not available to address this issue. Conversely, the delay in surgery and hormonal therapy resulting from preoperative chemotherapy might have been detrimental in older women with ER-positive tumors. This might be particularly problematic for strongly ER-positive tumors with low recurrence scores and a low likelihood of responding to chemotherapy.[35]

It is also noteworthy that, in Protocol B-18, DFS conditional on being event free for 5 years demonstrated a nearly statistically significant benefit in favor of the preoperative chemotherapy group. This post hoc analysis revealing the separation of the DFS curves at approximately 5 years could be a reflection of an effect on ER-positive tumors, which have a greater risk for late recurrences, with 60% of the recurrences occurring after year 5. In contrast, ER-negative tumors have a higher risk of recurrence within the first 5 years.[36] Moreover, such an effect might also have contributed to the treatment-by-age interaction discussed earlier, with preoperative chemotherapy being preferentially beneficial at preventing late recurrences of ER-positive tumors in younger women, who did not receive any hormonal therapy in B-18. Whether this would have been a strictly cytotoxic effect or perhaps a benefit from earlier ovarian suppression in the preoperative group less than 50 years old is also a matter of conjecture. Thus, the combination of late and age-related benefit of preoperative chemotherapy may result from the benefit of earlier chemotherapy in younger patients with ER-negative tumors and a decrease in late recurrences of ER-positive tumors in women who did not receive tamoxifen. Furthermore, as noted earlier, delaying surgery while giving ineffective chemotherapy may have been detrimental in older women.

Women participating in B-27 were slightly younger at study entry, had larger tumors, and had a higher proportion of clinically positive nodes than did women in B-18. Despite these adverse characteristics, an analysis adjusted for baseline characteristics indicated that women in B-27 had significantly better outcomes on average than women in B-18. This may reflect other improvements in patient treatment, including the addition of taxane, the use of tamoxifen in premenopausal patients, and more effective hormonal therapy options.

These long-term data from NSABP B-18 and B-27 continue to demonstrate that the achievement of pCR in the breast and negative axillary nodes after preoperative therapy clearly predict favorable long-term outcomes. However, most patients will not achieve a pCR with neoadjuvant chemotherapy. In addition, significant heterogeneity exists in terms of outcomes among non-pCR patients after preoperative therapy. For example, in NSABP B-27, among women who did not achieve a pCR, the 8-year DFS was 70% for patients with negative nodes compared with 40% for patients with four to nine positive nodes. Conversely, some patients with chemotherapy-nonresponsive tumors may nevertheless do well, perhaps because their tumors are slow growing or because of effective hormonal therapy.[35]

It is imperative that efforts continue, to develop molecular markers of response to predict patients who will achieve a pCR and patients who will have a favorable prognosis despite not achieving a pCR. Published data demonstrate that gene expression profiles can be predictors of a pCR in the neoadjuvant setting.[35] Gene expression profiles from B-27 are being evaluated for prediction of outcomes in patients who did not achieve a pCR with neoadjuvant chemotherapy (S. Paik, personal communication, March 2007). This may help to identify those non-pCR patients who might benefit from new therapies and those who will do well despite a non-pCR. Furthermore, other methods have been proposed to quantitate the residual tumor burden and to predict patient outcomes after neoadjuvant therapy.[37,38] Development and validation of predictive markers for outcomes of patients treated with neoadjuvant therapy will be critical for achieving optimal benefit from these therapies. Overall, preoperative chemotherapy is equivalent to adjuvant chemotherapy with respect to OS and DFS; however, it may be beneficial for patients who desire breast conservation but are not good candidates at presentation. Moreover, despite the weakness of pCR as a surrogate for OS and DFS in the detection of a treatment effect, preoperative chemotherapy may be valuable for addressing research questions about breast cancer biology and response to treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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ERRATA

The September 10, 2006, article by Gordon et al entitled, "Clinical Activity of Pertuzumab (rhuMAb 2C4), a HER Dimerization Inhibitor, in Advanced Ovarian Cancer: Potential Predictive Relationship With Tumor HER2 Activation Status" (J Clin Oncol 24:4324-4332, 2006) contained errors.

In Table 3, the data were incorrectly given for Survival and Progression Free Survival. The corrected table is reprinted below in its entirety. The online version has been corrected in departure from the print.

Table 3. Clinical Efficacy of Pertuzumab in Patients in Cohort 1 by Tumor pHER2 Status

	pHER2+		pHER2−		Unknown		All Patients	
	No.	%	No.	%	No.	%	No.	%
Total	8	100.0	20	100.0	27	100.0	55	100.0
PR	1	12.5	0	0	1	3.7	2	3.6
SD ≥ 6 months	0	0	2*	10.0	2	7.4	4	7.3
SD < 6 months, CA-125 drops ≥ 50%	1	12.5	0	0	2	7.4	3	5.5
SD < 6 months, CA-125 drops ≥ 25% but < 50%	0	0	0	0	2	7.4	2	3.6
Other SD	5	62.5	3	15.0	7	25.9	15	27.3
PD	1	12.5	13	65.0	13	48.1	27	49.1
Unable to evaluate response	0	0	2	10.0	0	0	2	3.6
Survival, weeks								
Median	74.6		37.0		48.4		46.7	
95% CI	28.4 to NYR		18.6 to NYR		21.6 to 82.1		30.4 to 66.6	
PFS, weeks								
Median	20.9		5.8		9.1		7.6	
95% CI	11.1 to 24.6		5.3 to 10.6		6.1 to 12.1		6.0 to 11.4	

NOTE. Clinical activity was defined as PR + SD ≥ 6 months + SD with CA-125 drop ≥ 50%. Nine patients (15.0%) in cohort 1 achieved clinical activity. Of the 20 pHER2− patients, 13 had PD (65.0%), whereas the incidence of PD in pHER2+ patients was one (12.5%) of eight. The overall incidence of pHER2+ in 34 ELISA assessable tumors was 29.4% (10 of 34), but only eight of 10 pHER2+ patients were assessable for clinical efficacy.

Abbreviations: pHER2, phosphorylated HER2; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression free survival.

*One patient also had a CA-125 drop ≥ 50%.

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The February 10, 2008, review article by Rastogi et al entitled, "Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27" (J Clin Oncol 26:778-785, 2008) contained errors. In Figure 1 and Figure 4, the abscissas (*x*-axes) were labeled as "Time After Surgery (years)," whereas they should have been labeled as "Time After Random Assignment (years)." The online version has been corrected in departure from the print.

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