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 Tumors: Results From the National Surgical Adjuvant Breast and Bowel Project B-15

By Bernard Fisher, Ann M. Brown, Nikolay V. Dimitrov, Roger Poisson, Carol Redmond, Richard G. Margolese, David Bowman, Norman Wolmark, D. Lawrence Wickerham, Carl G. Kardinal, Henry Shibata, A.H.G. Paterson, Carl M. Sutherland, Nicholas J. Robert, Phyllis Joyce Ager, Lawrence Levy, Janet Wolter, Timothy Wozniak, Edwin R. Fisher, and Melvin Deutsch

The National Surgical Adjuvant Breast and Bowel Project (NSABP) implemented protocol B-15 to compare 2 months of Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH) and cyclophosphamide (AC) with 6 months of conventional cyclophosphamide, methotrexate, and fluorouracil (CMF) in patients with breast cancer nonresponsive to tamoxifen (TAM, T). A second aim was to determine whether AC followed in 6 months by intravenous (IV) CMF was more effective than AC without reinduction therapy. Through 3 years of follow-up, findings from 2,194 patients indicate no significant difference in disease-free survival (DFS, $P = .5$), distant disease-free survival (DDFS, $P = .5$) or survival (S, $P = .8$) among the three groups. Since the outcome from AC and CMF was almost identical, the issue arises concerning which regimen is more appropriate for the treatment of breast cancer patients. AC seems preferable since, following total mastectomy, AC was completed on day 63 versus day 154 for conventional CMF; patients visited health professionals three times as often for conventional CMF as for AC; women on AC received therapy on each of 4 days versus on each of 84 days for conventional CMF; and nausea-control medication was given for about 84 days to conventional CMF patients versus for about 12 days to patients on AC. The difference in the amount of alopecia between the two treatment groups was less than anticipated. While alopecia was almost universally observed following AC therapy, 71% of the CMF patients also had hair loss and, in 41%, the loss was greater than 50%. This study and NSABP B-16, which evaluates the worth of AC therapy in TAM-responsive patients, indicate the merit of 2 months of AC therapy for all positive-node breast cancer patients.

J Clin Oncol 8:1483-1496. © 1990 by American Society of Clinical Oncology.

INITIAL EVIDENCE to indicate that systemic adjuvant chemotherapy could alter the natural history of patients with primary operable breast cancer and no evidence of metastatic disease came from the first randomized clinical trial (B-01) conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP).[1,2] That study, implemented in 1958, compared the outcome of patients who received thiotepa on the day of operation and on each of the first 2 postoperative days with the outcome of those given placebo. The results indicated that disease-free survival (DFS) and survival (S) could be altered by chemotherapy and that the response to chemotherapy was heterogeneous. However, these findings were, for the most part, ignored because they failed to meet physicians' expectations that all patients would be cured by the therapy. Not until 1972 was another major randomized trial begun to evaluate the worth of adjuvant chemotherapy. That trial (B-05), also carried out by the NSABP, compared patients who received melphalan (L-PAM), on 5 consecutive days every 6 weeks for 2 years with those who had been given placebo.[3] As was demonstrated with thiotepa, the findings showed a significant improvement in

From the National Surgical Adjuvant Breast and Bowel Project Headquarters, Pittsburgh, PA.

Submitted October 30, 1989; accepted March 26, 1990.

Supported by Public Health Service grants from the National Cancer Institute (NCI-U10-CA-12027, NCI-U10-CA-37377, and NCI-U10-CA-39086) and by a grant from the American Cancer Society (ACS-R-13).

Address reprint requests to the National Surgical Adjuvant Breast and Bowel Project Headquarters, Room 914, Scaife Hall, 3550 Terrace St, Pittsburgh, PA 15261.

0732-183X/90/0809-0010$3.00/0

DFS and S among women ≤ 49 years of age who had been treated with L-PAM. Results of a trial subsequently conducted in Milan, Italy, in which women treated with a course of cyclophosphamide, methotrexate, and fluorouracil (CMF) every month for 1 year were compared with an untreated group of patients, also showed a benefit from the chemotherapy.[4] A later study by the same investigators indicated that CMF given over a 6-month period produced a benefit at least as good as that obtained from 12 months of the same therapy.[5] Consequently, CMF became the most frequently used adjuvant treatment for patients with positive axillary nodes.

During the next decade, other major trials conducted by the NSABP and other investigators throughout the world established convincingly the worth of a variety of multiagent chemotherapeutic regimens for the treatment of primary breast cancer. Among the findings obtained from NSABP studies was evidence to indicate that the advantage observed from administering tamoxifen (TAM) with chemotherapy was associated with tumor estrogen (ER) and progesterone receptor (PgR) content as well as patient age and nodal status.[6] Consequently, patient populations could be identified as being either TAM "nonresponsive" or TAM "responsive." The former group consisted of all patients aged ≤ 49 years and those 50 to 59 years with a tumor PgR less than 10 fmol, regardless of ER. All other women constituted the TAM-responsive group. We have recently reported the worth of using doxorubicin (Adriamycin [A]; Adria Laboratories, Columbus, OH) in those patient cohorts. In one NSABP study (B-11), TAM-nonresponsive patients who received doxorubicin in addition to L-PAM and fluorouracil (PAF) were found to have a significantly better DFS and S through 6 years of follow-up than patients who received the two-drug combination without doxorubicin.[7] In another study (B-16), the use of TAM and short-course Adriamycin-cyclophosphamide (AC) therapy (completed in 63 days) resulted in an outcome better than that achieved by TAM alone in positive-node patients aged ≥ 50 years with tumors responsive to TAM.[8]

Findings from NSABP studies, as well as those of others, have generally indicated that if a benefit in DFS is to result from adjuvant chemotherapy it is apt to become evident in the first year or so of follow-up, with the advantage likely to result from the first few cycles of treatment. Administration of drug beyond that point is more likely to produce greater toxicity without certainty that a better outcome will result. If further benefit is to be derived from the use of chemotherapy, effort must be directed toward improving on as well as sustaining the initial gain achieved. The present study was designed to determine the benefit of short-course, intensive chemotherapy administered after operation both with and without reinstituting a different chemotherapeutic regimen 6 months after completion of the initial therapy.

NSABP clinical trial B-15 was conducted to compare the worth of 2 months of AC with 6 months of conventional CMF in breast cancer patients considered to be nonresponsive to TAM. A second aim was to determine whether, in the same patient population, AC therapy followed 6 months later by reinduction chemotherapy with parenteral CMF (AC → intravenous [IV] CMF) would be more effective than AC without reinduction therapy. This report provides the initial findings from the B-15 study.

METHODS

Women with primary operable breast cancer and at least one histologically verified positive axillary node were eligible for this study if they fulfilled specific criteria common to all NSABP clinical trials evaluating systemic therapy[3,9] and if they were considered to have TAM-nonresponsive tumors. Criteria for TAM-nonresponsiveness, defined in terms of age and/or PgR status, were derived from a previous NSABP trial (B-09) in which patients aged ≤ 49 years and those 50 to 59 years having tumors with a PgR level less than 10 fmol/mg of cytosol protein, regardless of ER status,[6] failed to respond any more favorably to a combination of L-PAM, 5-FU and TAM (PFT) than to L-PAM and 5-FU (PF) alone. Women aged 50 to 59 years having tumors with a PgR level ≥ 10 fmol, regardless of ER, and all patients 60 to 70 years of age, regardless of ER or PgR, were defined as TAM-responsive and were assigned to another trial, B-16, the results of which have been reported elsewhere.[8]

Tumor specimens were assayed for both ER and PgR levels by the sucrose density gradient, dextran-coated charcoal titration with Scatchard analysis, or dextran-coated charcoal with a single saturating dose. A requirement of the study was that ER and PgR be performed in laboratories that had complied with NSABP prerequisites for quality control.[10]

Patient accrual began on October 1, 1984, and was terminated on October 14, 1988. Following assignment to the study, patients were stratified according to number of positive nodes (one to three, four to nine, 10 or more), quantitative PgR level (< 50 and ≥ 50 fmol), and type of operation (total mastectomy and axillary dissection, or lumpectomy, axillary dissection and breast radiation). Randomization was performed within strata, using a biased-coin approach to ensure

treatment balance within an institution. Patients were randomized among three treatment arms. Therapy in all three groups was initiated between 2 and 5 weeks after operation. Patients in group I received AC therapy: Adriamycin 60 mg/m^2 IV, and cyclophosphamide 600 mg/m^2 IV, every 21 days for four cycles. Women in group II received AC therapy in doses identical to those administered to women in group I. Six months after the last course of AC chemotherapy, patients in group II received IV CMF: cyclophosphamide 750 mg/m^2 IV every 28 days for three cycles, methotrexate 40 mg/m^2 IV on days 1 and 8 every 28 days for three cycles, and 5-FU 600 mg/m^2 IV on days 1 and 8 every 28 days for three cycles. Patients in group III received conventional CMF: cyclophosphamide 100 mg/m^2 by mouth on days 1 through 14 every 28 days for six cycles, methotrexate 40 mg/m^2 IV on days 1 and 8 every 28 days for six cycles, and 5-FU 600 mg/m^2 IV on days 1 and 8 every 28 days for six cycles.

No dose reduction of Adriamycin or cyclophosphamide was allowed for patients receiving AC who developed hematologic or gastrointestinal toxicity. When hematologic toxicity occurred, administration of AC was delayed until granulocyte counts were ≥ 1,000 and platelet counts were ≥ 100,000. When gastrointestinal toxicity was present, the administration of AC was delayed until full dose could be tolerated. If patients required hospitalization because of a septic episode (defined as fever > 38.5°C and/or evidence of systemic infection in the presence of a lowered granulocyte count), all subsequent courses of Adriamycin and cyclophosphamide were to be given at 75% of the original calculated dose.

For patients receiving parenteral CMF reinduction therapy, no dose reduction was permitted in the therapy administered on day 1. Administration of the three drugs was delayed until granulocyte and platelet counts permitted giving a full dose. If on day 8 the granulocyte count was less than 1,000 or the platelet count was less than 100,000, day-8 doses were omitted. For patients who received conventional CMF, if the WBC count was less than 2,500 or the platelet count was less than 75,000 on day 1, therapy was delayed until the counts returned to ≥ 2,500 and ≥ 75,000, respectively, at which time 75% of the calculated dose was to be administered, or 100% of the dose if the WBC count was ≥ 3,500 and the platelet count was ≥ 100,000. If on day 8 the WBC count was less than 2,500 or the platelet count was less than 75,000, all day-8 doses were omitted. Appropriate dose reductions were used for gastrointestinal toxicity.

Before January 1985, all patients had total mastectomy and axillary dissection. At that time, findings from NSABP B-06 indicated the efficacy of lumpectomy plus axillary dissection and breast radiation.[11] As a result, patients who underwent that operative procedure also became eligible for this trial. (Details of lumpectomy plus axillary dissection and radiation therapy have been described elsewhere.[12]) In those women who received AC (groups I and II), radiation therapy was begun after the fourth cycle of AC when there was no evidence of hematologic toxicity and no later than 4 weeks after completion of chemotherapy. In patients randomized to conventional CMF (group III), radiation was begun after completion of the first course of CMF when there was no evidence of hematologic toxicity. Administration of the second course of CMF was delayed until completion of the 5 weeks of radiotherapy.

Data in this study were obtained from 2,194 eligible patients with follow-up information (Table 1). An additional 124 eligible patients had been randomized but were not included in the analyses because they had not been in the study long enough to have a follow-up report submitted to the NSABP Biostatistical Center. Only 20 of the 2,338 patients randomized were considered ineligible for the protocol. Results of analyses conducted with ineligible patients (seven in the AC group, seven in the AC → CMF group, and six in the CMF group) included and excluded were essentially the same; the results presented are with the 20 patients excluded. Reasons for patient ineligibility were multiple: four had disease that was too far advanced, seven had problems with obtaining tumor ER or PgR analyses, four had too lengthy a period between pathologic diagnosis and randomization, two had prior cancer, two had improper axillary dissection, and one had too long an interval between mastectomy and treatment. The average time on study for each of the three treatment groups was 26.2 months. Characteristics of the eligible patients with follow-up data as of December 31, 1988 are shown in Table 2. As expected, the attributes used as stratification factors are well balanced across the treatment groups; the attributes not used in the stratification are also well balanced due to the randomization process.

The percentage of patients who were disease-free, distant disease-free, or surviving through 36 months after surgery was estimated by the actuarial life-table method.[13] In analysis of DFS, an "event" is defined as the first documented evidence of local, regional, or distant recurrence, recurrence of tumor in the ipsilateral breast following lumpectomy, second primary cancer, or death without recurrence of cancer. Events for analysis of distant DFS (DDFS) include distant metastases as a first recurrence or following local or regional metastases, as well as second primary cancer. For overall S, death from any cause is the end point of interest.

The statistical significance of the difference between the life-table distributions by treatment was determined by a summary χ^2 (log-rank) statistic,[14] with adjustment for the three stratification variables. All P values relate to the entire

Table 1. Study Information

Patient Status	No. of Patients in Each Treatment Group: Group I AC	Group II AC→IV CMF	Group III Conventional CMF	Total No. of Patients
Randomized	781	781	776	2,338
Eligible	774	774	770	2,318
Eligible with follow-up	734	728	732	2,194
At 2 years	374	368	366	1,108
At 3 years	196	201	179	576
Average time on study (months)	26.2	26.2	26.2	26.2

Table 2. Patient and Tumor Characteristics

Characteristic*	Group I AC (N = 734) %	Group II AC→IV CMF (N = 728) %	Group III Conventional CMF (N = 732) %
Age (years)			
≤ 49	79	77	81
50–59	21	23	19
No. of positive nodes			
1–3	56	56	56
4–9	30	30	30
10 +	14	15	14
Operation			
Lumpectomy	27	28	27
Total mastectomy	73	72	73
Tumor ER (fmol)			
0–9	46	44	49
10–49	33	35	34
50–99	14	13	11
100 +	7	8	6
Tumor PgR (fmol)			
0–9	53	53	55
10–49	17	16	14
50–99	9	10	9
100 +	21	21	22
Pathologic tumor size (cm)			
0–2.0	28	28	29
2.1–5.0	48	46	44
≥ 5.1	8	7	8
Unknown	16	19	19

NOTE. From eligible patients with follow-up as of December 31, 1988.

*Values are percentage of patients in the treatment groups.

period of observation and are not truncated at 36 months. Two-sided P values below .05 are considered statistically significant. There is adequate power to detect a 10% difference in DFS and a 7% difference in S at 3 years after mastectomy.

Adjusted curves for DFS, DDFS, and S were computed using the summary relative odds method[15] with CMF designated as the reference group for the adjusted curves. The curves were plotted on a logarithmic scale in which the slope of the curve represents the rate of failure over time. Multivariate analysis using the Cox proportional hazards model[16] was undertaken to adjust for prognostic factors and to test for possible treatment-covariate interactions. There were no significant interactions.

The percentage of patients who experienced selected toxicities is shown for all eligible or ineligible individuals with toxicity information on file at the time of analysis. Patients who experienced more than one grade of a side effect have been classified according to their greatest toxicity. Patients who experienced less toxicity than the selected grades have been omitted. Since a different number of courses of therapy was administered to patients in each of the three groups, the number of courses associated with a specified toxicity is also presented to demonstrate the actual incidence.

The protocol-stipulated amount of each of the drugs to be administered per patient, as well as the amount actually received, is expressed as milligrams per square meter. The protocol-stipulated dose intensity to be administered to each patient, as well as the dose intensity of the amount received, is expressed as milligrams per square meter per month. In lumpectomy-treated patients who received conventional CMF, analysis of dose intensity took into account the interruption of chemotherapy to allow for administration of radiation therapy. Since no similar interruption occurred following total mastectomy, data relative to total dose and dose intensity are presented separately for the total mastectomy and lumpectomy patients. For CMF reinduction, the body-surface area used to calculate total dose and dose intensity was that determined at the time of the first course of reinduction therapy rather than that determined at the time of randomization. These analyses were restricted to patients randomized in the first 3 years of the protocol to allow adequate time for submission and processing of treatment information. The results are presented as both the median percentage of the protocol-specified amount of drug received and as percentage of patients who received either ≥ 80% or ≥ 95% of the protocol-specified dose and dose intensity.

Factors causing total dose to be less than the full amount as specified by the protocol include treatment failure, discontinuance of therapy, protocol-specified omissions due to toxicity, and lack of adherence to protocol specifications. When conventional CMF was used, protocol-specified dose reductions due to toxicity could affect total dosage. Such was not the case, however, when AC or reinduction CMF therapy was used since no dose reductions due to toxicity were permitted.

Factors affecting dose intensity include protocol-specified delays or omissions due to toxicity, lack of adherence to protocol specifications, and, for conventional CMF, protocol-specified dose reductions due to toxicity. Neither treatment failure nor discontinuance of therapy affects dose intensity because the dose-intensity measure relates only to the period of time during which a drug is actually received.

RESULTS

DFS, DDFS, and S

Simultaneous comparison of the three treatment groups using life-table analyses through 3 years of follow-up indicated no significant difference in DFS ($P = .5$), DDFS ($P = .5$), or S ($P = .8$) among the three groups (Fig 1). The outcome of patients who received four courses of AC therapy given over 63 days was virtually identical to the outcome of patients who received six courses of conventional CMF given over 154 days when patients were treated by total mastectomy and over 190 days when lumpectomy and breast radiation was performed. At 3 years, the DFS was 62% for patients who received AC and 63% for patients treated with CMF, the DDFS was 68% for both groups, and the S 83% and 82%, respectively. The group of patients who received CMF reinduction therapy 6 months after treatment with AC had a slightly, but not significantly, better 3-year DFS (68%) than after AC alone ($P = .5$) or CMF ($P = .2$). No such

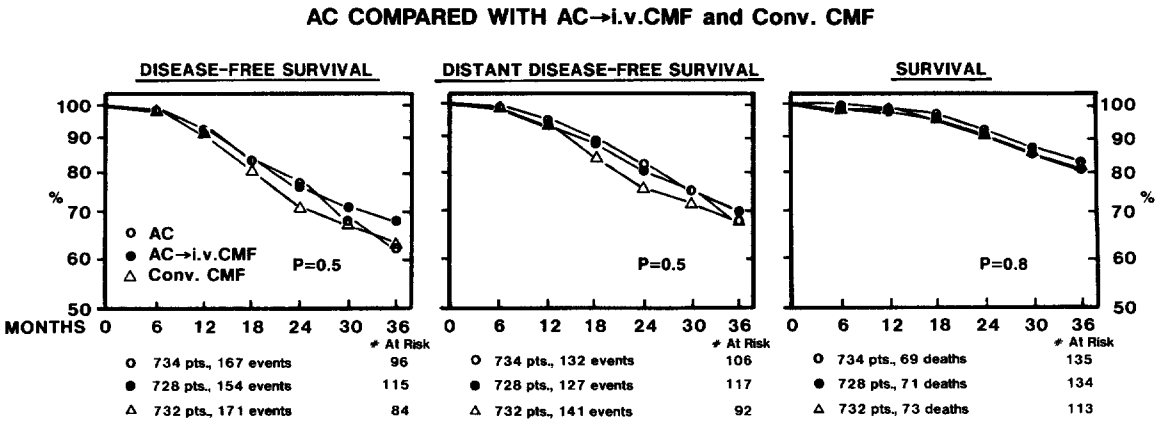

Fig 1. Outcome of patients on AC with and without reinduction IV CMF compared with outcome of patients on conventional CMF.

difference in DDFS or S was evident. When a comparison of DFS, DDFS, and S was made among patients in the three treatment groups treated by total mastectomy, no significant difference in any of the three outcomes was observed ($P = .6$, .6, and .9, respectively; Fig 2). Similar findings were obtained when the comparisons were made among patients in the three groups treated by lumpectomy and breast radiation, a circumstance that required that the second and subsequent courses of conventional CMF be delayed until completion of the radiation.

Sites of Treatment Failure

The distribution of first sites of treatment failure in the various treatment groups is pre-

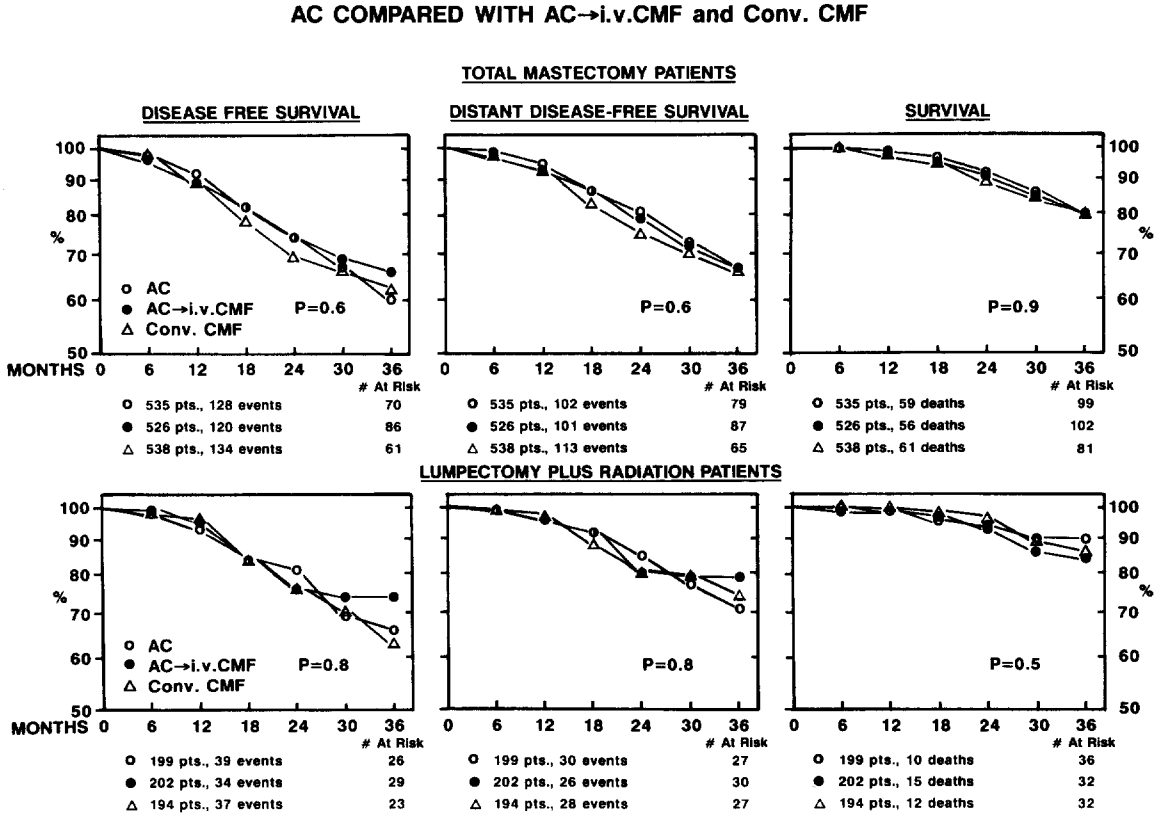

Fig 2. Outcome of patients according to operative therapy received: total mastectomy or lumpectomy plus breast radiation.

sented in Table 3. The findings fail to indicate at this time that one regimen is more effective than another in reducing the incidence of first treatment failure at a particular site.

Toxicity

Information regarding severity of toxicity, ie, the maximum toxicity per patient, is summarized in Table 4. For the 1,492 patients treated with AC, the average number of courses received at the time of compilation of the data was 3.8 of a possible four. For the 509 patients treated with CMF reinduction therapy, the average number of courses of IV CMF was 2.8 of three. For the 739 women treated with conventional CMF, the average number of courses received was 5.5 of the protocol-required six courses. Myelosuppression was slightly less serious after AC therapy than after CMF, as were nausea without vomiting, diarrhea, hemorrhagic cystitis, and weight gain. On the other hand, patients who received AC therapy were more likely to experience vomiting (76%) than were their counterparts on conventional CMF (39%). Vomiting was also likely to be more severe in the AC-treated patients. Alopecia was more severe following AC than after conventional CMF. Whereas 92% of AC-treated patients had hair loss, 71% of those treated with conventional CMF were reported to have lost some hair. The loss was at least 50% in 89% of the patients who received AC and 41% in those receiving conventional CMF. Only 14% of the patients who received reinduction CMF suffered that extent of alopecia. No deaths occurred while patients were receiving protocol therapy. Three cases of blood dyscrasia were reported, one in each of the three protocol groups (AC alone, AC with CMF reinduction, and conventional CMF).

Table 3. Location of First Site of Treatment Failure

Site of Recurrence	Group I AC (N = 734) No.	Group II AC → IV CMF (N = 728) No.	Group III Conventional CMF (N = 732) No.
Local-regional	64	54	61
Ipsilateral breast*	6	11	5
Chest wall	25	13	14
Scar	5	6	6
Axilla	7	8	10
Supraclavicular node	10	9	12
More than one	11	7	14
Distant	92	94	103
Opposite breast†	5	10	12
Skeletal	40	37	31
Respiratory	19	12	20
Other	28	35	40
Combinations	7	2	4
Local and distant	4	1	2
Regional and distant	1	0	2
Unknown	2	1	0
Second primary‡	2	2	2
Dead without breast cancer	2	2	1
Alive, event-free	567	574	561

*In patients treated by lumpectomy.
†Includes second cancers.
‡Except opposite breast

Information on the incidence of selected toxicities for each treatment regimen, specifically the number of courses in which each type of toxicity was reported per 100 patients receiving that regimen, is presented in Table 5. Gastric distress during AC therapy was observed in 290 courses per 100 patients, in 175 courses per 100 patients after CMF reinduction therapy, and in 294 courses per 100 patients in those who received conventional CMF. Patients experienced nausea without attendant vomiting more frequently in the six-course conventional CMF than in the four-course AC or three-course CMF reinduction regimens. Vomiting was reported more often in the AC regimen. Diarrhea was a more common complaint when conventional CMF was administered. Although patients who receive conventional CMF are somewhat more likely to experience neurologic toxicity (eight courses per 100 patients *v* four courses per 100 patients), the difference is accounted for by grade 1 toxicity (transient incoordination). There is little difference between AC and conventional CMF for the other toxicities shown in Table 5.

Information on courses of therapy delayed because of hematologic or gastrointestinal toxicity according to the drug combination used is summarized in Table 6. These data relate to delayed courses, regardless of the number of delays per course. However, very few courses were delayed more than 1 week, and delays were most often the result of hematologic rather than gastrointestinal toxicity. The percentage of courses delayed and the percentage of patients having delayed courses were greatest following conventional CMF; the fewest delays occurred following CMF reinduction therapy.

Amount of Drug Received

The total protocol dose (milligrams per square meter) and dose intensity (milligrams per square

Table 4. Severity of Toxicity: Greatest Toxicity per Patient

	Group I AC (N = 1492) %	Group II Reinduction IV CMF (N = 509) %	Group III Conventional CMF (N = 739) %
WBC			
Grade 3 (1,000–1,999)	3.4	5.1	9.4
Grade 4 (< 1,000)	0.3	0	0.3
Platelets			
Grade 3 (25,000–49,999)	0	0.2	0.3
Grade 4 (< 25,000)	0.1	0	0
Nausea and vomiting			
Nausea only	15.5	20.2	42.8
Vomiting ≤ 12 hours	34.4	38.9	25.2
Vomiting > 12 hours	36.8	16.9	12.0
Intractable	4.7	1.0	1.6
Diarrhea			
> 4 stools/day	2.6	2.6	4.5
Hemorrhage with dehydration	0.3	0	0.3
Death	0	0	0
Alopecia			
Thinning < 50%	3.0	23.0	30.8
Incomplete > 50%	19.9	8.3	25.5
Complete	69.5	5.9	15.1
Cardiovascular-functional			
Asymptomatic	0.2	0	0.1
Transient	0.1	0.2	0
Symptomatic	0.1	0	0
Nontreatment responsive	0	0	0
Death	0	0	0
Phlebitis			
Superficial	0.5	0.2	1.1
Deep	0.1	0	0.3
Embolism	0.1	0	0.3
Death	0	0	0
Infection			
Systemic	0.9	0.4	0.3
Shock, sepsis	1.5	1.2	0.9
Death	0	0	0
Hemorrhagic cystitis			
Mild	0.3	0.4	1.6
Severe	0	0	0.1
Weight gain			
5%–10%	10.6	24.8	27.9
10%–20%	2.1	12.2	12.0
> 20%	1.7	2.0	2.3
Weight loss			
5%–10%	6.2	5.3	5.7
10%–20%	1.4	1.8	2.3
> 20%	1.0	0.6	0.5
Fever			
Moderate (38°C–40°C)	5.1	2.2	3.2
Severe (> 40°)	0.4	0.4	0.3
Total no. courses	5,676	1,416	4,068
Average no. per patient	3.8	2.8	5.5

Table 5. Incidence of Toxicity

Toxicity	Group I AC	Group II Reinduction IV CMF	Group III Conventional CMF
Nausea without vomiting	84*	64	211
Vomiting	206	111	83
Diarrhea	39	25	65
Stomatitis	54	41	51
Neurologic toxicity	4	3	8
Skin reaction	10	5	11
Fever	10	4	7
Infection	16	11	16
No. of courses	5,676	1,416	4,068
No. of patients	1,492	509	739
Courses/patient	3.8	2.8	5.5
Courses/regimen	4.0	3.0	6.0

*Number of courses with specified toxicity per 100 patients.

Table 6. Delay in Therapy Administration Because of Hematologic or Gastrointestinal Toxicity

Attribute	Group I AC	Group II Reinduction IV CMF	Group III Conventional CMF
No. of patients with course information	1,492*	509	739
No. of courses	5,676	1,416	4,068
Delayed courses			
No.	342	63	408
%	6.0	4.4	10.0
Patients with delayed courses			
No.	233	50	234
%	15.6	9.8	31.7

*AC only plus AC portion of AC → CMF.

meter per month) of each drug and the median percentages received are shown in Table 7. The median dose of AC received by the AC-treated patients in groups I and II was almost 100% of the full protocol-defined dose. In those women treated by conventional CMF (group III), the median amount of drug received was about 90% of the full protocol amount, and in those given IV CMF reinduction therapy (group II), the median amount of drug received was about 98% for each of the three drugs in the combination. For all drugs in each of the combinations administered, the median percentage of the protocol dose intensity received was approximately the same as the corresponding median percentage of the total protocol dose received. There was little difference in the median percentage of the total dose or dose intensity of the drugs received in the conventional CMF combination following either total mastectomy or lumpectomy plus breast irradiation.

More patients on AC therapy received at least 80% of the protocol-prescribed amount than did the patients on CMF reinduction or conventional CMF therapy (Table 8). There was little difference between CMF reinduction and conventional CMF at the 80% level. For each drug in each combination, the percentage of patients who received ≥ 80% of the protocol-specified dose intensity was approximately the same as the percentage of patients who received at least 80% of the protocol-specified dose. Patients assigned to AC therapy were less likely to receive 95% of the specified dose intensity than 95% of the total

Table 7. Total Protocol Dose and Dose Intensity and Median Percentage Received

Measurement		Group I AC (N = 558)		Group II AC → IV CMF (N = 556)		Group III Conventional CMF TM (N = 413)		Group III Conventional CMF L + XRT (N = 142)	
		Protocol Amount	Median % Received	Protocol Amount	Median % Received	Protocol Amount	Median % Received	Protocol Amount	Median % Received
AC Adria	mg/m²*	240	99.8	240	99.8	—	—	—	—
	mg/m²/mo‡	87	98.9	87	98.3	—	—	—	—
AC cyclo	mg/m²	2,400	99.7	2,400	99.6	—	—	—	—
	mg/m²/mo	867	98.9	867	98.7	—	—	—	—
CMF cyclo	mg/m²	—	—	2,250	98.0	8,400	87.6	8,400	88.3
	mg/m²/mo	—	—	813	97.9	1,517	87.0	1,174	89.1
CMF MTX	mg/m²	—	—	240	99.6	480	91.7	480	92.1
	mg/m²/mo	—	—	87	95.5	87	90.5	67	91.7
CMF 5-FU	mg/m²	—	—	3,600	98.4	7,200	90.9	7,200	91.7
	mg/m²/mo	—	—	1,300	93.7	1,300	88.5	1,007	90.8

Abbreviations: Adria, Adriamycin; cyclo, cyclophosphamide; MTX, methotrexate; TM, total mastectomy; L + XRT, lumpectomy plus breast irradiation.

*mg/m² = total dose.

‡mg/m²/mo = intensity.

Table 8. Percentage of Patients Receiving Specified Amount of Full Protocol Dose and Full Dose Intensity

Amount of Drug Received	Drug	Group I AC (N = 558)		Group II AC → IV CMF (N = 556)		Group III Conventional CMF TM (N = 413)		Group III Conventional CMF L + XRT (N = 142)	
		mg/m²	mg/m²/mo	mg/m²	mg/m²/mo	mg/m²	mg/m²/mo	mg/m²	mg/m²/mo
≥ 80%	AC Adria	89	93	85	89	—	—	—	—
	AC cyclo	89	92	84	90	—	—	—	—
	CMF cyclo	—	—	71	75	64	66	70	70
	CMF MTX	—	—	69	70	74	73	77	83
	CMF 5-FU	—	—	69	69	71	71	75	76
≥ 95%	AC Adria	84	66	78	64	—	—	—	—
	AC cyclo	84	66	77	64	—	—	—	—
	CMF cyclo	—	—	65	58	29	27	30	34
	CMF MTX	—	—	54	51	41	38	44	44
	CMF 5-FU	—	—	55	51	38	32	39	42

NOTE. mg/m² = total dose; mg/m²/mo = intensity.

dose, since the protocol mandated treatment delays for toxicity but not dose reductions. The difference between dose and dose intensity at the 95% level was less pronounced with CMF reinduction and did not occur with conventional CMF for which dose reductions rather than delays were specified for moderate toxicity. Despite the disparity between dose and dose intensity, patients on AC were more likely to receive ≥ 95% of both dose and dose intensity than were patients on either conventional CMF or CMF reinduction. The percentage of patients receiving ≥ 95% of the protocol dose intensity was somewhat higher for those on conventional CMF treated with lumpectomy and breast radiation than with total mastectomy.

Compliance With Reinduction Therapy

Information regarding acceptance of reinduction therapy was obtained from patients who were randomized to AC → CMF as of December 31, 1987 (Table 9). Patients entered on study during 1988 have been omitted because of either insufficient time to allow for completion of AC therapy and the 6-month rest period or because of inadequate time to obtain treatment information. Of the 610 randomized patients, 87 (14%) were not eligible for reinduction therapy for reasons summarized in Table 9. Over half (7.9%) of these were ineligible because of a prior event such as a treatment failure, second cancer, or death from causes other than cancer. Only 5% of those who were eligible for IV CMF therapy failed to start treatment.

DISCUSSION

This report indicates that the DFS, DDFS, S, and first sites of treatment failure of patients treated with AC are nearly identical to those obtained following administration of conventional CMF. Thus, the issue arises as to which of the two regimens might be more appropriate for use as the control group in a new clinical trial or for the treatment of patients unable to participate in clinical trials. Since CMF is currently the most commonly used regimen for treatment of stage II breast cancer and is, consequently, the one with which physicians are most familiar, the findings are likely to be viewed as providing support for the continued use of conventional CMF. On the other hand, information from this study (B-15), as well as findings from other NSABP clinical trials using Adriamycin, provide justification for seriously considering replace-

Table 9. Compliance With Reinduction Therapy

Patient Information	No. of Patients	% of Patients
Randomized through 12/31/87	610	100
Ineligible for reinduction therapy, IV CMF (at 9 months)	87	14
Prior event	48	(7.9)
Discontinued AC	18	(3.0)
Never started AC	9	(1.5)
Protocol ineligible	6	(1.0)
Consent withdrawal	2	(0.3)
Other reasons	4	(0.7)
Eligible for reinduction therapy, IV CMF (at 9 months)	523	86
Started reinduction	495	81
Failed to start	28	5

ment of CMF with AC. The fact that AC administration is completed on day 63 of therapy, whereas the last dose of CMF is not given until the 154th day of treatment when total mastectomy has been performed and even later (about 190 days) following lumpectomy and breast irradiation, is a strong recommendation for the use of the AC regimen. A further reason for using AC is that patients who receive that drug combination usually see a physician or other health care professional only four times to receive drugs, whereas patients on CMF are seen 12 times for that purpose. In addition, a woman on AC therapy has a personal responsibility for seeing that she takes chemotherapy on each of only 4 days, whereas, if she is the recipient of CMF, she is obligated to be certain that she receives some or all of the drugs on each of 84 days. In addition to these quality-of-life considerations, it has been found that the toxicity resulting from the 2 months of AC therapy compares favorably with the side effects associated with the 6 months of conventional CMF.

Despite the fact that CMF has been widely used for more than a decade, a meticulously documented, detailed account of the toxicity resulting from the regimen is lacking, particularly one that characterizes the experience of a large group of physicians who have used the therapy as originally described. This report provides such information, including not only the maximum toxicity per patient (severity) for both CMF and AC but also the number of courses in each type of toxicity experienced (incidence) in both regimens. While the incidence of gastric distress was remarkably similar in both the AC and conventional CMF regimens (290 courses per 100 patients in the former and 294 courses per 100 patients in the latter), the nature of the distress differed.

Nurses who participated in the currently reported study have estimated that almost all CMF-treated women required medication to control nausea and other side effects throughout each 14-day course of therapy, ie, for about 84 days. In contrast, such medication is administered to patients on AC for only 12 days, ie, for about 3 days after each course. While vomiting was more common after AC therapy, myelosuppression, diarrhea, hemorrhagic cystitis, and weight gain occurred more often following the administration of conventional CMF. There was little difference between the two groups in the frequency of other toxicities except for alopecia, which has always been considered to be a temporarily vexing side effect of Adriamycin therapy. It has not been as well appreciated that hair loss following CMF occurs with the frequency in which it was observed in this study: 71% of patients had some alopecia, and, in 41%, hair loss of greater than 50% occurred. Because of the relatively short follow-up, this report cannot address the equivalence of the two regimens relative to long-term toxicities, eg, cardiac or myeloproliferative disorders.

Information obtained from two additional analyses provides support for use of the AC regimen. Both of these analyses indicate that toxicity makes compliance with CMF administration more difficult. The first analysis showed that delays and dose reductions occurred more frequently when CMF was used than when AC was used. Both the percentage of treatment courses delayed and the percentage of patients having delayed courses because of hematologic or gastrointestinal toxicity were greater following treatment with conventional CMF than with AC. In the second analysis, when the median amount of drug received was examined either according to the amount per square meter of body surface or according to the amount per square meter of body-surface area per month (intensity), it was found that the median percentage of total drug dose received was lower in patients receiving CMF than in those on AC. Moreover, it was found that a greater percentage of patients on AC therapy received a larger percentage of the total protocol-defined amount of drug, either milligrams per square meter or milligrams per square meter per month, than did patients on CMF.

When this study was designed, there was concern regarding the appropriateness of administering breast radiation to lumpectomy patients simultaneously with chemotherapy.[17-20] Several investigators had recommended either giving one or two courses of chemotherapy before the radiation therapy and then completing the chemotherapy subsequent to the irradiation, or modifying the CMF given during radiation by deleting the methotrexate and then restoring that drug to the combination in the courses given after irradiation. Concern with cosmesis, hematologic toxic-

ity, and the ability to deliver protocol-stipulated doses of drugs prompted such modifications. Thus, in this study, all lumpectomy patients randomized to conventional CMF received radiation therapy after completion of the first course of CMF; the five additional courses were given subsequent to completion of radiation. In patients treated by total mastectomy, the six courses of CMF were given without interruption. No evidence was obtained to indicate that the interruption of conventional CMF therapy by radiation therapy affected the outcome of patients receiving that regimen. Regardless of whether lumpectomy plus breast radiation or total mastectomy was performed, the median percentage of the total protocol-prescribed dose (milligrams per square meter) or the total protocol-prescribed intensity (milligrams per square meter per month) of each of the drugs received by patients treated by the conventional CMF combination was similar.

The advantage we recently reported resulting from the addition of Adriamycin to L-PAM and 5-FU (PAF) in the NSABP study B-11 without consequential side effects attributable to that drug further attests to the safety and effectiveness of Adriamycin.[7] In that study, not only was there a highly significant benefit in DFS following use of the drug in 344 patients who were similar to those in the B-15 study, ie, patients who were TAM-nonresponsive, but the Adriamycin added little hematologic toxicity, cardiac toxicity, or other side effect of consequence, either during or subsequent to completion of the therapy. We have also recently observed in NSABP B-16 that the addition of AC, as used in B-15, to TAM in women with TAM-responsive stage II breast cancer resulted in a significantly better DFS than that which occurred following the use of TAM alone.[7] The side effects resulting from the use of AC in that trial were similar to those reported in B-15.

The demonstrated efficacy of AC in both TAM-responsive and TAM-nonresponsive patients indicates that there is justification for the use of AC therapy in all pre- or postmenopausal breast cancer patients with positive axillary nodes, as well as in all breast cancer patients with tumors that are either ER-negative or ER-positive. As a consequence of these findings, AC is currently being used in NSABP protocols evaluating the worth of preoperative chemotherapy (B-18) and in a stage II study (B-22) evaluating the efficacy of (1) intensifying the dose of cyclophosphamide (keeping the total dose of the drug similar to that currently used, ie, 2,400 mg/m^2, but administering it over two courses [1,200 mg/m^2 each] instead of four); and (2) not only intensifying the dose but also increasing the total cumulative dose by administering 1,200 mg/m^2 at each of four courses, for a total of 4,800 mg/m^2. Findings from B-22 will be significant in determining whether administering increasing amounts of a drug for even shorter periods of time than is currently being done may be more efficacious.

In order to test the value of reinduction therapy in this study, a rest period rather than immediate sequencing of regimens was used. Since there was no information available regarding tumor cell growth kinetics—either directly or from modeling—which could aid us in determining the time interval to be used for administering a putatively noncross-resistant regimen (parenteral CMF), we resorted to information obtained by our examination of hazard functions obtained from a previous generation of NSABP protocols. These data led us to use the 6-month interval between the completion of the AC therapy and the onset of the parenteral CMF.

There was concern that patients who had undergone previous treatment with adjuvant therapy (AC) would be reluctant to receive additional therapy, particularly after their hair had grown back and they were completely asymptomatic. That concern was not realized, in that 95% of patients eligible for the reinduction therapy complied by initiating it. These patients were readily managed, and it was generally agreed that fewer undesirable effects resulted from IV CMF therapy than were observed from the use of conventional CMF. Of particular interest in that regard was the observation that less hair loss occurred following parenteral CMF than following conventional CMF or AC therapy. As with conventional CMF, weight gain relative to weight at randomization was reported to have occurred in about 40% of patients. Sufficient follow-up time has not yet elapsed to allow for the presentation of findings to indicate the worth of the reinduction chemotherapy as used in this study.

ACKNOWLEDGMENT

We acknowledge the contribution of Tanya Spewock in the preparation of this manuscript.

APPENDIX
Institutions Contributing Ten or More Patients to This Study

Principal Investigator	Institution
Robert W. Sponzo, MD	Albany Regional Cancer Center, Albany, NY
Ajit Desai, MD	Albert Einstein Medical Center, Philadelphia, PA
David Prager, MD	Allentown Hospital, Allentown, PA
Karl K. Boatman, MD	Baptist Medical Center, Oklahoma City, OK
William S. Blakemore, MD	Baptist Medical Centers, Birmingham, AL
William Reed, MD, and Charles F. White, MD	Baystate Medical Center, Springfield, MA
Jesse Spector, MD	Berkshire Medical Center, Pittsfield, MA
David B. Myers, MD	Billings Interhospital Oncology Project, Billings, MT
Maureen T. Kavanah, MD	Boston University, Boston, MA
John Michael Sterchi, MD	Bowman Gray School of Medicine, Winston-Salem, NC
Reginald Pugh, MD	Community Clinical Oncology Program, Allegheny-Singer Research Corp, Pittsburgh, PA
Carl G. Kardinal, MD	Community Clinical Oncology Program, Alton Ochsner Medical Foundation, New Orleans, LA
Jerry T. Guy, MD	Community Clinical Oncology Program, Columbus, OH
James S. Ungerleider, MD	Community Clinical Oncology Program, Dayton, OH
James R. Borst, MD	Community Clinical Oncology Program, Grand Rapids, MI
H. James Wallace, Jr, MD	Community Clinical Oncology Program, Green Mountain Oncology Group, Green Mountain, VT
James L. Hoehn, MD	Community Clinical Oncology Program, Marshfield Clinic, Marshfield, WI
Julian B. Hill, MD	Community Clinical Oncology Program, North Mississippi, Tupelo, MS
Phyllis Joyce Ager, MD	Community Clinical Oncology Program, San Joaquin Valley, Fresno, CA
Steven Jubelirer, MD	Community Clinical Oncology Program, West Virginia, Charleston, WV
José Terz, MD	City of Hope Medical Center, Duarte, CA
A. H. G. Paterson, MD	Cross Cancer Institute, Edmonton, Canada
Spencer O. Raab, MD	East Carolina University, Greenville, NC
James Evans, MD	Geisinger Medical Center, Danville, PA
Richard Welling, MD	Good Samaritan Hospital, Cincinnati, OH
David State, MD	Harbor General Hospital, Torrance, CA
Peter Deckers, MD	Hartford Hospital, Hartford, CT
André Robidoux, MD	Hotel-Dieu, Montreal, Canada
Yosef H. Pilch, MD	Illinois Masonic Medical Center, Chicago, IL
Richard G. Margolese, MD	Jewish General Hospital, Montreal, Canada
Andrew G. Glass, MD	Kaiser Permanente, Portland, OR
Marvin Nicola, MD	Kaiser Permanente, San Diego, CA
Martin Potvin, MD	L'Hopital Laval, Quebec City, Canada
Isidore Cohn, Jr, MD	Louisiana State University, New Orleans, LA
Lee Smith, MD	Mid-Atlantic Oncology Program, Hematology Oncology Associates, Alexandria, VA
John Gullo, MD	Mid-Atlantic Oncology Program, Hematology Oncology Associates, Syracuse, NY
David Bowman, MD	Manitoba Cancer Foundation, Winnipeg, Canada
Peter D. Eisenberg, MD	Marin General Hospital, Greenbrae, CA
Timothy Wozniak, MD	Medical Center of Delaware, Inc, Newark, DE
Walter Lawrence, MD	Medical College of Virginia, Richmond, VA
David Plotkin, MD	Memorial Cancer Research Foundation, Los Angeles, CA
Richard Desser, MD	Michael Reese Hospital, Chicago, IL
Nikolay V. Dimitrov, MD	Michigan State University, E Lansing, MI
Richard G. Rosen, MD	Montefiore Hospital and Medical Center, Bronx, NY
Michael Thirlwell, MD	Montreal General Hospital, Montreal, Canada
Richard Bornstein, MD and Lawrence Levy, MD	Mount Sinai Medical Center, Cleveland, OH
Frederick J. Meyers, MD	Northern California Cancer Center/Northern California Oncology Group, University of California, Davis, CA
Leo Stolbach, MD	New England Deaconess Hospital, Boston, MA
Alan J. Lippman, MD	Newark Beth Israel Medical Center, Newark, NJ
Daniele J. Perrault, MD	Ottawa Regional Cancer Centre, Ottawa, Canada
Harvey J. Lerner, MD	Pennsylvania Hospital, Philadelphia, PA
Charles J. Lusch, MD	Reading Hospital and Medical Center, West Reading, PA
Henry Shibata, MD	Royal Victoria Hospital, Montreal, Canada

(continued on following page)

APPENDIX

Institutions Contributing Ten or More Patients to This Study (Cont'd)

Principal Investigator	Institution
Janet Wolter, MD	Rush Presbyterian-St Luke's Medical Center, Chicago, IL
Roger Poisson, MD	St Luc Hospital, Montreal, Canada
Alan N. Morrison, MD	St Luke's Hospital, Bethlehem, PA
John R. Keyserlingk, MD	St Mary's Hospital Center, Montreal, Canada
Leo Mahoney, MD	St Michael's Hospital, Toronto, Canada
Jean Couture, MD	St Sacrement Hospital, Quebec City, Canada
Nicholas LiCalzi, MD	South Nassau Communities Hospital, Long Island, NY
A. Robert Thiessen, MD	Tacoma General Hospital, Tacoma, WA
Brian Pruitt, MD	Texas Tech Medical School, Amarillo, TX
Nicholas Robert, MD	Tufts University, New England Medical Center, Boston, MA
Carl M. Sutherland, MD	Tulane University, New Orleans, LA
Neil Abramson, MD	University of Florida, Blood and Cancer Center, Jacksonville, FL
Robert Oishi, MD	University of Hawaii, Honolulu, HI
Peter Jochimsen, MD	University of Iowa, Iowa City, IA
Edward H. Romond, MD	University of Kentucky, Lexington, KY
Joseph C. Allegra, MD	University of Louisville, Louisville, KY
E. George Elias, MD, PhD	University of Maryland, Baltimore, MD
Alfred S. Ketcham, MD	University of Miami, Miami, FL
Bernard Fisher, MD	University of Pittsburgh, Pittsburgh, PA
Anatolio B. Cruz, Jr, MD	University of Texas, San Antonio, TX
Roger S. Foster, Jr, MD	University of Vermont, Burlington, VT

REFERENCES

1. Fisher B, Ravdin RG, Ausman RK, et al: Surgical adjuvant chemotherapy in cancer of the breast: Results of a decade of cooperative investigation. Ann Surg 168:337-356, 1968

2. Fisher B, Slack N, Katrych D, et al: Ten-year follow-up results of patients with carcinoma of the breast in a cooperative clinical trial evaluating surgical adjuvant chemotherapy. Surg Gynecol Obstet 140:528-534, 1975

3. Fisher B, Carbone P, Economou SG, et al: L-phenylalanine mustard (L-PAM) in the management of primary breast cancer: A report of early findings. N Engl J Med 292:117-122, 1975

4. Bonadonna G, Brusamolino E, Valagussa P, et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405-410, 1976

5. Tancini G, Bonadonna G, Valagussa P, et al: Adjuvant CMF in breast cancer: Comparative 5-year results of 12 versus 6 cycles. J Clin Oncol 1:2-10, 1983

6. Fisher B, Redmond C, Brown A, et al: Influence of tumor estrogen and progesterone receptor levels on the response to tamoxifen and chemotherapy in primary breast cancer. J Clin Oncol 1:227-241, 1983

7. Fisher B, Redmond C, Wickerham DL, et al: Doxorubicin-containing regimens for the treatment of Stage II breast cancer: The NSABP experience. J Clin Oncol 7:572-582, 1989

8. Fisher B, Redmond C, Legault-Poisson S, et al: Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive-node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: Results from the National Surgical Adjuvant Breast and Bowel Project B-16. J Clin Oncol 8:1005-1018, 1990

9. Fisher B, Glass A, Redmond C, et al: L-phenylalanine mustard (L-PAM) in the management of primary breast cancer: An update of earlier findings and a comparison with those utilizing L-PAM plus 5-fluorouracil (5-FU). Cancer 39:2883-2903, 1977

10. Witliff JL, Fisher B, Durant JR: Establishment of uniformity in steroid receptor analyses used in cooperative clinical trials of breast cancer treatment, in Henningsen B, Linder F, Steichele C (eds): Recent Results in Cancer Research, vol 71. New York, NY, Springer-Verlag, 1980, pp 198-206

11. Fisher B, Bauer M, Margolese R, et al: Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in treatment of breast cancer. N Engl J Med 312:665-673, 1985

12. Fisher B, Wolmark N, Fisher ER, et al: Lumpectomy and axillary dissection for breast cancer: Surgical, pathological and radiation considerations. World J Surg 9:692-698, 1985

13. Cutler SJ, Ederer F: Maximum utilization of the life-table method in analyzing survival. J Chronic Dis 8:699-712, 1958

14. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

15. Hankey BF, Myers MH: Evaluating differences in survival between two groups of patients. J Chronic Dis 24:523-531, 1971

16. Cox DR: Regression models and life-tables. JR Stat Soc (B) 34:187-220, 1972

17. Botnick LE, Lange R, Come S, et al: Primary breast irradiation and concomitant adjuvant chemotherapy, in Harris JR, Hellman S, Silen W (eds): Conservative Management of Breast Cancer, New Surgical and Radiotherapeutic Techniques. Philadelphia, PA, Lippincott, 1982, pp 321-328

18. Glick JH, Weiler C, Danoff BF, et al: Adjuvant chemotherapy in patients undergoing definitive irradiation for primary breast cancer—The University of Pennsylvania experience, in Harris JR, Hellman S, Silen W (eds): Conservative Management of Breast Cancer, New Surgical and Radiotherapeutic Techniques. Philadelphia, PA, Lippincott, 1982, pp 311-320

19. Lichter AS, d'Angelo TM, Lippman ME, et al: Adjuvant chemotherapy in patients treated primarily with irradiation for localized breast cancer, in Harris JR, Hellman S, Silen W (eds): Conservative Management of Breast Cancer, New Surgical and Radiotherapeutic Techniques. Philadelphia, PA, Lippincott, 1982, pp 299-310

20. Danoff BF, Goodman RL, Glick JH, et al: The effect of adjuvant chemotherapy on cosmesis and complications in patients with breast cancer treated by definitive irradiation. Int J Rad Onc Biol Phys 9:1625-1630, 1983