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Breast Cancer Adjuvant Chemotherapy Dosing in Obese Patients: Dissemination of Information from Clinical Trials to Clinical Practice

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Abstract

Background—Substantial variations in adjuvant breast cancer chemotherapy dosing in obese women suggests that there is uncertainty about optimal practices in these patients. The purpose of this study was to investigate variations in dose determinations in clinical trial protocols and publications over the last three decades as potential sources of this uncertainty.

Methods—We used the National Cancer Institute database to identify protocols of breast cancer adjuvant chemotherapy conducted by cooperative groups between 1970 - 2000 and obtained the protocols directly from the cooperative groups. We categorized dose determinations in each protocol and in published reports from each clinical trial. Fisher's exact tests were used to compare the proportions of protocols that used full weight based doses over time.

Results—Protocol-specified chemotherapy dosing was obtained for all of 44 eligible trials. We identified a significant increase in the use of full weight-based doses in the later time period compared to the earlier (p value = 0.004, two-sided Fisher's exact test). A notable exception is one cooperative group that continues to require dose limitations for doxorubicin and cyclophosphamide in patients with a body surface area over 2.0 m². Regardless of publication date, published reports of clinical trials rarely provide information on use of full or limited weight-based doses.

Conclusions—Variations in dose determinations among clinical trial protocols and lack of information on use of full weight-based doses in most publications are two likely sources of variation in chemotherapy dosing in obese women. Developing consensus and disseminating information about optimal chemotherapy dosing will likely reduce such variation and may improve survival among obese patients with breast cancer.

Keywords

Breast cancer; obesity; clinical trials; practice variations; practice guidelines

Introduction

Chemotherapy doses in the adjuvant treatment of breast cancer are generally normalized to body size using the patient's body surface area (BSA). The BSA is in turn calculated using height and weight according to one of several methods.¹ Although the majority of overweight and obese women are treated with full weight-based chemotherapy doses, the practice of administering reduced doses (compared to those doses that would be expected if actual weight were used to calculate chemotherapy) in heavy women is common.²⁻⁵ For example, in a national study of patients treated in 901 practices with adjuvant chemotherapy for breast cancer between 2002 and 2005, 13.8% of overweight patients, 17.7% of obese patients, and 26.6% of severely obese women received initial dose reductions of more than 15% when compared to doses that would have been given had full weight-based dosing been used. Reduced doses were not explained by age, comorbidity, and other clinical factors.⁶ The use of reduced doses varies according to treating physician² and even according to geographic region.⁶ Such practice variation suggests that there is uncertainty about the optimal dosing of chemotherapy, including perhaps the safety and necessity of using actual body weight when calculating chemotherapy doses. Uncertainty clearly persists despite compelling evidence that full weight-based doses are not only safe but also necessary if the full benefit of chemotherapy is to be achieved.⁷⁻⁹

The purpose of the current study was to answer the following questions: 1) How have cooperative groups specified that chemotherapy doses be determined in obese patients? That is, do protocols specify the use of full weight-based doses or a dosing limit? (2) Is there variation between cooperative groups in how chemotherapy doses are determined? (3) How much information is available on chemotherapy dose determinations in published manuscripts from cooperative group trials?

The premise of this study is that clinical trial protocols provide a standard of care for prescribing physicians with respect to such issues as dose determinations in studies of non-myeloablative chemotherapy. A second premise is that physicians use the published medical literature to inform their chemotherapy prescribing decisions and that lack of information on dosing contributes to uncertainty about best chemotherapy dosing practices in the treatment of obese women.

Methods

Dose determinations in cooperative group clinical trials are not compiled in a central source, and publications rarely provide information on dosing limits (see below). Primary data collection thus involved retrieving study protocols from cooperative groups in the United States and in Europe. We used the Physician Data Query (PDQ) of the National Cancer Institute (NCI) to identify all registered and completed cooperative group non-myeloablative adjuvant breast cancer chemotherapy clinical trials. The search, which was conducted in

August 2005 and repeated in April 2007, was limited to closed protocols that enrolled female patients with stage I, II, or III breast cancer and used chemotherapy. We did not limit by geographic location or trial activation date. Each trial in the generated set of trials was individually examined and required to meet the following criteria. We only included adjuvant non-myeloablative chemotherapy trials that were authored by one or more cooperative groups. Myeloablative regimens requiring stem cell support or bone marrow support were excluded because the doses of chemotherapy used in myeloablative regimens are generally several-fold higher than those used in standard adjuvant regimens, and there is little information on safety of full weight-based doses in this setting. The only remaining inclusion criteria for each trial was the publication of a manuscript or manuscripts that reported patient survival using the data of no more than two clinical trials. Protocols were requested from each cooperative group in writing.

Dosing instructions were categorized into one of three categories: 1) full weight-based dosing, 2) dose adjustment or maximum limit in heavy patients (ideal or corrected body weight used to calculate BSA or a maximum BSA “cap”), or 3) no specific instructions.

Permission was obtained from either the cooperative group Chair or Disease Site Chair of the cooperative group to publish information on the details of protocol-specified dose determinations and limits.

We searched PubMed, Ovid, the NCI database, the cooperative group websites, and the Dana Farber Cancer Institute database to identify a published paper for each trial that focused on outcomes. In cases where more than one paper reported on outcomes, one paper was selected at random. For each paper, dose determinations in obese patients were categorized into one of the three categories described above.

Fisher's exact test was used to compare the proportions of trials that specified use of full weight-based dosing (no dose limits) over the study time period and to compare the proportion of published studies that provided information on the use of full doses versus dose limits.

Permission was obtained from either the cooperative group Chair or Disease Site Chair of the cooperative group to publish information on the details of protocol-specified dose determinations and limits.

Results

Clinical Trial Protocols

Search criteria generated 44 eligible clinical trials from the NCI database spanning the years 1970 through 2000. The dosing instructions were successfully obtained for all. The included protocols are listed in Table 1.

Eleven (25%) of the protocols used actual body weight in dose determinations. Nineteen (43%) specified some form of dose limits, whether through use of ideal body weight, the lesser of actual or ideal body weight, adjusted ideal body weight, or a BSA limit of 2.0 m². Dose determinations changed over time (Figure 1) and were more likely to be specified in

later protocols. Of the 22 protocols initiated through December 1984, 21 (95%) either did not directly address dose determinations in heavy patients ($n = 9$) or specified dose reduction ($n = 12$) in heavy patients. One trial specified use of actual body weight in dose determinations. Of the 22 protocols initiated after 1984, 10 (45%) specified full weight-based dosing, 7 (32%) specified dose limits, and 5 (23%) provided no specific information on chemotherapy dosing in heavy patients. The difference in the use of full weight based doses in the two time periods was significant (p value = 0.004, two-sided Fisher's exact test). All of the protocols from that required dose limits were authored by one cooperative group and specified dose limits only for cyclophosphamide and doxorubicin; no dose limitations were specified for the taxanes. The four remaining U.S. cooperative groups required full weight-based doses in protocols initiated after 1984.

Clinical Trial Publications

Information on chemotherapy dose determinations in the published clinical trial reports corresponding to the cooperative group protocols is shown in Figure 2. Of the 43 published papers (one paper reported on the findings of two trials, see Table 2), information on dose determination in heavy patients was included in only 10 (23%). Dosing information was provided in 8 (42%) of the 19 publications from studies that specified dose limits compared with only 2 (18%) of the 11 that used actual weight-based doses, but this difference is not statistically significant (two-sided Fisher's exact test p value = 0.25).

Discussion

Early cooperative group protocols included in the Physician Data Query of the National Cancer Institute (NCI) used dose limits or did not address dosing practices in obese patients. Over the last two decades, all but one of the United States cooperative groups, and one of the two European cooperative groups have specified use of actual body weight with no dose limitations in trial participants. Information on dosing practices is generally lacking in the published reports of these clinical trials.

A substantial body of research supports the use of full weight-based doses in heavy patients receiving adjuvant chemotherapy for breast cancer.⁷⁻¹⁴ There is no evidence that use of actual body weight to determine chemotherapy doses is associated with greater myeloid or non-myeloid toxicity.^{2, 7-12} Moreover, receipt of full weight-based doses appears to be required for patients, particularly those with estrogen receptor-negative tumors, to achieve the full benefit of chemotherapy.^{7, 9} For example, in one clinical trial of adjuvant chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil, obese patients who had a 5% or greater reduction in chemotherapy doses below those expected if actual body weight were used had inferior failure-free survival.⁷ Likewise, in a pooled analysis of four adjuvant chemotherapy trials, obese patients with hormone receptor-negative breast cancer who received less than 85% of full weight-based doses had inferior disease-free and overall survival.⁹ Based on the available evidence, the Southwestern Oncology Group (SWOG) generated a written policy in 2001 (Siu-Fun Wong, PhD, personal communication) that actual body weight should always be used in calculating treatment doses in patients participating in clinical trials. The Cancer and Leukemia Group B (CALGB) considers

failure to use actual body weight in the calculation of drug doses to be a major protocol deviation.

Despite the evidence against dose limits in heavy patients receiving adjuvant breast cancer chemotherapy, many obese and overweight patients receive reduced chemotherapy doses as described above.²⁻⁵ The present-day practice of limiting adjuvant chemotherapy doses in heavy patients and the finding that use of reduced chemotherapy doses varies according to provider suggests that there is persistent uncertainty about best practices in this patient population. The fact that the protocols of one of the largest cooperative groups specify dose limits of cyclophosphamide and doxorubicin suggests that uncertainty may also exist between clinical trialists.

Dose determinations specified within clinical trial protocols may serve as a form of guideline for chemotherapy dosing in heavy patients even in patients being treated “off protocol.” The lack of information on chemotherapy dosing in most of the corresponding published manuscripts further indicates that physicians may not have sufficient information about standard practices in the dosing of obese patients. Without specific information to the contrary, a physician may elect to fall back on older practices of limiting doses in the heavy patient.

Our study is restricted to published cooperative group trials registered in the Physician Data Query. The findings of this survey thus cannot be generalized to all published clinical trials of adjuvant breast cancer chemotherapy. Nonetheless, cooperative group trials are highly influential and their publications widely-cited.

We contend that the present-day variations in chemotherapy dosing in heavy patients represent unwarranted variation.¹⁵ Developing and disseminating standards for dose determinations in heavy patients is critical in decreasing variation in dosing practices and may improve outcomes among obese women. As the prevalence of obesity and severe obesity increases,¹⁶ we suggest that cooperative groups come to consensus about dose determinations in obese patients based on the existing evidence and that guidelines development groups and biomedical journals provide specific information about the standard of care in dosing obese patients receiving adjuvant breast cancer chemotherapy.¹⁷

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7. Rosner GL, Hargis JB, Hollis DR, et al. Relationship between toxicity and obesity in women receiving adjuvant chemotherapy for breast cancer: Results from Cancer and Leukemia Group B Study 8541. *J Clin Oncol.* 1996; 14:3000–3008. [PubMed: 8918498]
8. Smith TJ, Desch CE. Neutropenia-wise and pound-foolish: Safe and effective chemotherapy in massively obese patients. *South Med J.* 1991; 84:883–885. [PubMed: 2068631]
9. Colleoni M, Li S, Gelber RD, et al. Relation between chemotherapy dose, oestrogen receptor expression, and body-mass index. *Lancet.* 2005; 366:1108–1110. [PubMed: 16182899]
10. Poikonen P, Blomqvist C, Joensuu H. Effect of obesity on the leukocyte nadir in women treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil dosed according to body surface area. *Acta Oncol.* 2001; 40:67–71. [PubMed: 11321664]
11. Poikonen P, Saarto T, Lundin J, Joensuu H, Blomqvist C. Leucocyte nadir as a marker for chemotherapy efficacy in node-positive breast cancer treated with adjuvant CMF. *Br J Cancer.* 1999; 80:1763–1766. [PubMed: 10468293]
12. Jenkins P, Elyan S, Freeman S. Obesity is not associated with increased myelosuppression in patients receiving chemotherapy for breast cancer. *Eur J Cancer.* 2006; 43:544–548. [PubMed: 17169553]
13. Baker SD, Grochow LB, Donehower RC. Should anticancer drug doses be adjusted in the obese patient? *J Natl Cancer Inst.* 1995; 87:333–334. [PubMed: 7853411]
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17. Michie S, Johnston M. Changing clinical behaviour by making guidelines specific. *BMJ.* 2004; 328:343–345. [PubMed: 14764503]

Figure 1.

Dose instructions for cooperative group clinical trials. Each shape represents 1 of 44 protocols, 1970 – 2001. The timeline beneath represents 5-year intervals. The included protocols are listed in Table 1.

● = full weight-based doses

○ = dose reduction (includes dose adjustment by use of ideal body weight, less or ideal or actual body weight, adjusted ideal body weight, or “capping” at 2 m²)

X = not specified in the protocol

	Number of Publications							
CALGB	7		○○	X●	●	X	X	
ECOG	8		○○	X○○○	X	X		
FRE-FNCLCC	2					X	X	
IBCSG	4				XXX	X		
NCCTG	1							X
NSABP	16	○	XXX	XXXX ¹	XXXX	X	XX	X
SWOG	5		XX	X	X	X		
Year		1970	1975	1980	1985	1990	1995	2000

¹ Publication reports on results of two protocols

Figure 2.

Dose determination instructions for each of 43 publications. The timeline beneath represents 5 year intervals. Dates indicate the date the trial began to enroll patients. Publication dates are available in Table 2.

● = full weight-based doses

○ = dose reduction (includes dose adjustment by use of ideal body weight, less or ideal or actual body weight, adjusted ideal body weight, or “capping” at 2 m²)

X = not specified

TABLE 1**Breast Cancer Adjuvant Chemotherapy Protocols**

Cooperative Group	Protocol Number	Year Accrual Began
Cancer and Leukemia Group B	7581	1975
	7784	1978
	8082	1980
	8443	1984
	8541	1985
	9344	1994
	9741	1997
Eastern Cooperative Oncology Group	5177	1978
	6177	1978
	1180	1980
	3181	1982
	4181	1982
	5181	1982
	5188	1989
North Central Cancer Treatment Group	3189	1990
	N9831	2000
National Surgical Adjuvant Breast and Bowel Project	B-05	1972
	B-07	1975
	B-09	1977
	B-10	1977
	B-11	1981
	B-12	1981
	B-13	1981
	B-15	1984
	B-16	1984
	B-18	1988
	B-19	1988
	B-20	1988
	B-22	1989
	B-23	1991
	B-27	1995
	B-28	1995
	B-31	2001
Southwest Oncology Group	7436	1975
	7827	1979
	8313	1983
	8897	1989

Cooperative Group	Protocol Number	Year Accrual Began
	9313	1994
Fédération Nationale des Centres de Lutte Contre le Cancer	GFEA-09	1993
	PACS-01	1997
International Breast Cancer Study Group	VI	1986
	VII	1986
	VIII	1990
	IX	1988

TABLE 2

Breast Cancer Adjuvant Chemotherapy Publications

Cancer and Leukemia Group B (CALGB)

Tormey DC, Weinberg VE, Holland JF, et al: A randomized trial of five and three drug chemotherapy and chemoimmunotherapy in women with operable node positive breast cancer. *J Clin Oncol* 1:138-45, 1983 (**CALGB 7581**)

Perloff M, Lesnick GJ, Korzun A, et al: Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: a Cancer and Leukemia Group B study. *J Clin Oncol* 6:261-9, 1988 (**CALGB 7784**)

Budman DR, Korzun AH, Aisner J, et al: A feasibility study of intensive CAF as outpatient adjuvant therapy for stage II breast cancer in a cooperative group: CALGB 8443. *Cancer Invest* 8:571-5, 1990 (**CALGB 8443**)

Wood WC, Budman DR, Korzun AH, et al: Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. *N Engl J Med* 330:1253-9, 1994 (**CALGB 8541**)

Perloff M, Norton L, Korzun AH, et al: Postsurgical adjuvant chemotherapy of stage II breast carcinoma with or without crossover to a non-cross-resistant regimen: A Cancer and Leukemia Group B study. *J Clin Oncol* 14:1589-98, 1996 (**CALGB 8082**)

Citron ML, Berry DA, Cirincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/ Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 21:1431-9, 2003 (**CALGB 9741**)

Henderson IC, Berry DA, Demetri GD, et al: Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 21:976-83, 2003 (**CALGB 9344**)

Eastern Cooperative Oncology Group (ECOG)

Taylor SGt, Kalish LA, Olson JE, et al: Adjuvant CMFP versus CMFP plus tamoxifen versus observation alone in postmenopausal, node-positive breast cancer patients: Three year results of an Eastern Cooperative Oncology Group study. *J Clin Oncol* 3:144-54, 1985 (**ECOG 6177**)

Mansour EG, Gray R, Shatila AH, et al: Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer. An intergroup study. *N Engl J Med* 320:485-90, 1989 (**ECOG 1180**)

Tormey DC, Gray R, Gilchrist K, et al: Adjuvant chemohormonal therapy with cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone (CMFP) or CMFP plus tamoxifen compared with CMF for premenopausal breast cancer patients. An Eastern Cooperative Oncology Group trial. *Cancer* 65:200-6, 1990 (**ECOG 5177**)

Falkson HC, Gray R, Wolberg WH, et al: Adjuvant trial of 12 cycles of CMFPT followed by observation or continuous tamoxifen versus four cycles of CMFPT in postmenopausal women with breast cancer: An Eastern Cooperative Oncology Group phase III study. *J Clin Oncol* 8:599-607, 1990 (**ECOG 4181**)

Tormey DC, Gray R, Abeloff MD, et al: Adjuvant therapy with a doxorubicin regimen and long-term tamoxifen in premenopausal breast cancer patients: An Eastern Cooperative Oncology Group trial. *J Clin Oncol* 10:1848-56, 1992 (**ECOG 5181**)

Olson JE, Neuberg D, Pandya KJ, et al: The role of radiotherapy in the management of operable locally advanced breast carcinoma: Results of a randomized trial by the Eastern Cooperative Oncology Group. *Cancer* 79:1138-49, 1997 (**ECOG 3181**)

Fetting JH, Gray R, Fairclough DL, et al: Sixteen-week multidrug regimen versus cyclophosphamide, doxorubicin, and fluorouracil as adjuvant therapy for node-positive, receptor-negative breast cancer: An Intergroup study. *J Clin Oncol* 16:2382-91, 1998 (**ECOG 3189**)

Davidson NE, O'Neill AM, Vukov AM, et al: Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: Results from INT 0101 (E5188). *J Clin Oncol* 23:5973-82, 2005 (**ECOG 5188**)

Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)

Roche H, Fumoleau P, Spielmann M, et al: Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: The FNCLCC PACS 01 Trial. *J Clin Oncol* 24:5664-71, 2006 (**FRE-FNCLCC-PACS-01**)

Kerbrat P, Roche H, Bonnetterre J, et al: Epirubicin-vinorelbine vs FEC100 for node-positive, early breast cancer: French Adjuvant Study Group 09 trial. *Br J Cancer* 96:1633-8, 2007 (**FRE-FNCLCC-GFEA-09**)

International Breast Cancer Study Group (IBCSG)

Duration and reintroduction of adjuvant chemotherapy for node-positive premenopausal breast cancer patients. International Breast Cancer Study Group. *J Clin Oncol* 14:1885-94, 1996 (**IBCSG VI**)

Effectiveness of adjuvant chemotherapy in combination with tamoxifen for node-positive postmenopausal breast cancer patients. International Breast Cancer Study Group. *J Clin Oncol* 15:1385-94, 1997 (**IBCSG VII**)

Endocrine responsiveness and tailoring adjuvant therapy for postmenopausal lymph node-negative breast cancer: A randomized trial. *J Natl Cancer Inst* 94:1054-65, 2002 (**IBCSG IX**)

Castiglione-Gertsch M, O'Neill A, Price KN, et al: Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: A randomized trial. *J Natl Cancer Inst* 95:1833-46, 2003 (**IBCSG VIII**)

North Central Cancer Treatment Group (NCCTG)

Perez EA, Suman VJ, Davidson NE, et al: Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. *J Clin Oncol* 22:3700-4, 2004 (**NCCTG-N9831**)

National Surgical Adjuvant Breast and Bowel Project (NSABP)

Fisher B, Carbone P, Economou SG, et al: 1-Phenylalanine mustard (L-PAM) in the management of primary breast cancer. A report of early findings. *N Engl J Med* 292:117-22, 1975 (**NSABP B-05**)

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* 39:2883-903, 1977 (**NSABP B-07**)

Fisher B, Redmond C, Brown A, et al: Treatment of primary breast cancer with chemotherapy and tamoxifen. *N Engl J Med* 305:1-6, 1981 (**NSABP B-09**)

Fisher B, Redmond C, Dimitrov NV, et al: A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor-negative tumors. *N Engl J Med* 320:473-8, 1989 (**NSABP B-13**)

Fisher B, Redmond C, Wickerham DL, et al: Doxorubicin-containing regimens for the treatment of stage II breast cancer: The National Surgical Adjuvant Breast and Bowel Project experience. *J Clin Oncol* 7:572-82, 1989 (**NSABP B-11, B-12**)

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* 8:1005-18, 1990 (**NSABP B-16**)

Fisher B, Brown A, Wolmark N, et al: Evaluation of the worth of corynebacterium parvum in conjunction with chemotherapy as adjuvant treatment for primary breast cancer. Eight-year results from the National Surgical Adjuvant Breast and Bowel Project B-10. *Cancer* 66:220-7, 1990 (**NSABP B-10**)

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

Fisher B, Dignam J, Mamounas EP, et al: Sequential methotrexate and fluorouracil for the treatment of node-negative breast cancer patients with estrogen receptor-negative tumors: eight-year results from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 and first report of findings from NSABP B-19 comparing methotrexate and fluorouracil with conventional cyclophosphamide, methotrexate, and fluorouracil. *J Clin Oncol* 14:1982-92, 1996 (**NSABP B-19**)

Fisher B, Anderson S, Wickerham DL, et al: Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-22. *J Clin Oncol* 15:1858-69, 1997 (**NSABP B-22**)

Fisher B, Brown A, Mamounas E, et al: Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 15:2483-93, 1997 (**NSABP B-18**)

Fisher B, Dignam J, Wolmark N, et al: Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. *J Natl Cancer Inst* 89:1673-82, 1997 (**NSABP B-20**)

Fisher B, Anderson S, Tan-Chiu E, et al: Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-23. *J Clin Oncol* 19:931-42, 2001 (**NSABP B-23**)

Bear HD, Anderson S, Brown A, et al: The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 21:4165-74, 2003 (**NSABP B-27**)

Mamounas EP, Bryant J, Lembersky B, et al: Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. *J Clin Oncol* 23:3686-96, 2005 (**NSABP B-28**)

Tan-Chiu E, Yothers G, Romond E, et al: Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 23:7811-9, 2005 (**NSABP B-31**)

Southwest Oncology Group (SWOG)

Glucksberg H, Rivkin SE, Rasmussen S, et al: Combination chemotherapy (CMFVP) versus L-phenylalanine mustard (L-PAM) for operable breast cancer with positive axillary nodes: A Southwest Oncology Group Study. *Cancer* 50:423-34, 1982 (**SWOG 7436**)

Rivkin SE, Green S, Metch B, et al: One versus 2 years of CMFVP adjuvant chemotherapy in axillary node-positive and estrogen receptor-negative patients: A Southwest Oncology Group study. *J Clin Oncol* 11:1710-6, 1993 (**SWOG 7827**)

Budd GT, Green S, O'Bryan RM, et al: Short-course FAC-M versus 1 year of CMFVP in node-positive, hormone receptor-negative breast cancer: An intergroup study. *J Clin Oncol* 13:831-9, 1995 (**SWOG 8313**)

Pierce LJ, Hutchins LF, Green SR, et al: Sequencing of tamoxifen and radiotherapy after breast-conserving surgery in early-stage breast cancer. *J Clin Oncol* 23:24-9, 2005 (**SWOG 8897**)

Linden HM, Haskell CM, Green SJ, et al: Sequenced compared with simultaneous anthracycline and cyclophosphamide in high-risk stage I and II breast cancer: Final analysis from INT-0137 (S9313). *J Clin Oncol* 25:656-61, 2007 (**SWOG 9313**)