Neoadjuvant Chemotherapy

Randomized clinical trials have demonstrated that while neoadjuvant systemic therapy downstages tumors and improves the chance for breast conservation, disease-free and overall survival seem to be similar to using treatment postoperatively. A new generation of neoadjuvant studies is evaluating a variety of strategies including dose-intensive chemotherapy, the addition of taxanes and the synergistic XT combination — capecitabine/docetaxel. The neoadjuvant setting is also being utilized to evaluate new systemic agents and predictors of tumor response, including DNA microarray analysis.

NSABP B-27 TRIAL: PHASE III RANDOMIZED STUDY OF PREOPERATIVE DOXORUBICIN AND CYCLOPHOSPHAMIDE (AC) VERSUS PREOPERATIVE AC FOLLOWED BY DOCETAXEL VERSUS PREOPERATIVE AC AND POSTOPERATIVE DOCETAXEL IN WOMEN WITH OPERABLE CARCINOMA OF THE BREAST

Closed Protocol

Eligibility	Clinically palpable, node-negative and node-positive breast cancer
ARM 1	AC x 4 + TAM ➜ SURGERY
ARM 2	AC x 4 + TAM ➜ T x 4 ➜ SURGERY
ARM 3	AC x 4 + TAM ➜ SURGERY ➜ T x 4

AC=doxorubicin/cyclophosphamide; T=docetaxel;
TAM=tamoxifen po x 5 years

Patients undergoing breast-conserving surgery received radiation therapy.

SOURCE: NSABP website, November 2002.

NSABP B-27: TYPE OF SURGERY AND PATHOLOGIC FINDINGS AFTER PREOPERATIVE CHEMOTHERAPY

	AC	AC ➜ T	P-value
Lumpectomy	61.4%	63.1%	p=0.70
Pathologic CR	13.7%	25.6%	p<0.001
Node-neg	50.7%	58.1%	p=0.0004
Deaths	2	6	
Grade 4 toxicity	10%	24%	

DERIVED FROM: NSABP Presentation, 2001 San Antonio Breast Cancer Symposium.

PHASE III RANDOMIZED STUDY OF NEOADJUVANT DOXORUBICIN, CYCLOPHOSPHAMIDE AND PACLITAXEL WITH OR WITHOUT FILGRASTIM (G-CSF) IN WOMEN WITH INFLAMMATORY OR LOCALLY ADVANCED BREAST CANCER

Open Protocol

Protocol ID: SWOG-S0012, CTSU
Projected Accrual: 350 patients (175 per arm)

Eligibility	Inflammatory or locally advanced breast cancer, Stage IIB or IIIA/B. ER-negative if disease is not inflammatory
ARM 1	AC q3w x 5 ➜ surgery
ARM 2	[A qw + Co qd + G-CSF] x 15 ➜ surgery

A=doxorubicin; C=IV cyclophosphamide; Co=oral cyclophosphamide; G-CSF=filgrastim ; T= Paclitaxel

Within 3-6 weeks after completion of chemotherapy, patients with stable or responsive disease undergo surgical resection of tumor and affected nodes.

Study Contact:
Georgiana Kehr Ellis, Chair
Tel: 206-288-2048
Southwest Oncology Group

SOURCE: NCI Physician Data Query, February 2003.

NSABP B-18: CLINICAL OUTCOME AND NINE-YEAR FOLLOW-UP OF 1,523 PATIENTS RECEIVING PREOPERATIVE AC VERSUS POSTOPERATIVE AC CHEMOTHERAPY

	Pre-op AC	Post-op AC
Lumpectomy	67%	60%
Pathologic Nodal Status		
Negative	59%	43%
Positive	41%	57%
Survival*	69%	70%
DFS*	55%	53%
IBTR *	10.7%	7.6%

DERIVED FROM: Fisher B et al. *J Clin Oncol* 1997;15:2483-2493.
*Wolmark N et al. *J Natl Cancer Inst Monogr* 2001;30:96-102.

NSABP TRIAL OF PREOPERATIVE DOXORUBICIN AND CYCLOPHOSPHAMIDE (AC) FOLLOWED BY DOCETAXEL VERSUS PREOPERATIVE AC FOLLOWED BY CAPECITABINE AND DOCETAXEL (XT)

Proposed Protocol

ARM 1	AC x 4 ➜ docetaxel x 4 ➜ surgery
ARM 2	AC x 4 ➜ docetaxel/capecitabine ➜ surgery

SOURCE: Eleftherios Mamounas, Personal Communication, November 2002.

PHASE III STUDY OF CHEMOTHERAPY AND SURGERY COMPARING ADJUVANT DOXORUBICIN FOLLOWED BY CMF (CYCLOPHOSPHAMIDE, METHOTREXATE AND FLUOROURACIL) VERSUS ADJUVANT DOXORUBICIN AND PACLITAXEL FOLLOWED BY CMF VERSUS PRIMARY DOXORUBICIN AND PACLITAXEL FOLLOWED BY CMF IN WOMEN WITH OPERABLE BREAST CANCER AND TUMOR GREATER THAN 2 CENTIMETERS

Open Protocol

Protocol IDs: EU-97001, INT-23/96
Projected Accrual: 450 patients per arm

Eligibility	Operable breast cancer with a tumor > 2 cm
ARM 1	Surgery ➜ A x 4 ➜ CMF x 4
ARM 2	Surgery ➜ AT x 4 ➜ CMF x 4
ARM 3	AT x 4 ➜ CMF x 4 ➜ Surgery

A=doxorubicin; T=paclitaxel

All patients have either mastectomy or breast-conserving surgery; patients with unclear surgical margins may have a second surgery (re-resection or total mastectomy) or radiotherapy. Lymph node dissection is performed up to at least the second level.

At the end of the combined surgery plus chemotherapy approach (arms I and II) or after surgery (arm III), ER/PR-positive patients receive tamoxifen x 5 years.

Study Contact: Gianni Bonadonna, Chair. Tel: 2-239-02352, Istituto Nazionale per lo Studio e la Cura dei Tumori

SOURCE: NCI Physician Data Query, February 2003.

POTENTIAL IMPACT OF NEOADJUVANT CHEMOTHERAPY ON BREAST CANCER MANAGEMENT

I view induction chemotherapy as a positive trend because you do not lose anything, and there is a higher likelihood of being able to do a lumpectomy with a much better cosmetic result. It also provides an *in vivo* chemosensitivity assay. This trend will also allow us to start looking at minimally invasive surgery to the primary tumor.

I predict that in the next decade we will move away from axillary node dissection. Sentinel node biopsy may be a transition maneuver in this regard, because people do not yet feel totally comfortable giving up the nodal status information. But once we start using systemic therapy first, the remaining question relates to treatment of what's left of the primary tumor. The research question then would be, Do you need to take the patient to the operating room at all?

— Eva Singletary, MD

RESPONSE RATES IN NSABP B-27

Preoperative doxorubicin/cyclophosphamide followed by docetaxel increased both the clinical and pathologic response rates compared to preoperative doxorubicin/cyclophosphamide alone. The clinical response rate increased from 85% to 91%, with the complete response rate improving from 40% to 65%. Of even greater importance, the pathologic response rate essentially doubled.

The median tumor size in B-27 was 4.5 cm; whereas, the median tumor size in B-18 was about 2.2 cm. Surprisingly, the pathologic response rate for doxorubicin/cyclophosphamide was the same in both trials, indicating that a tumor will respond to neoadjuvant chemotherapy regardless of its size. Since B-27 involved eight cycles of therapy, there may have been a natural selection to enroll higher-risk patients with larger tumors.

—Eleftherios Mamounas, MD

PROPOSED NEOADJUVANT CAPECITABINE/DOCETAXEL TRIAL

In light of the B-27 trial results, we are designing a neoadjuvant trial that will compare doxorubicin/cyclophosphamide followed by docetaxel with or without capecitabine. This trial is based on Dr O'Shaughnessy's study, which demonstrated that capecitabine/docetaxel improved survival in patients with metastatic breast cancer. Since B-27 established that preoperative docetaxel almost doubled the pathologic response rate, we want to see if adding capecitabine will further increase the pathologic response.

This trial will also assess many biomarkers, both before and after chemotherapy, with sequential core biopsies. We will attempt to identify molecular biomarkers, with DNA microarray and high through-put technology that can predict the response to chemotherapy.

We particularly want to determine if docetaxel is up-regulating thymidine phosphorylase. Based on data from B-18 and B-27, sentinel node biopsy alone will be allowed for patients with a pathologic complete response. We will evaluate whether neoadjuvant chemotherapy can reduce the extent of surgery, not only in the breast but also in the axilla.

—Eleftherios Mamounas, MD

SELECT PUBLICATIONS

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