Neoadjuvant Chemotherapy

Randomized clinical trials have demonstrated that while neoadjuvant chemotherapy often downstages tumors and improves the chance for breast conservation, disease-free and overall survival are similar to that of patients who undergo postoperative therapy. A new generation of neoadjuvant studies is evaluating a variety of strategies, including dose-dense chemotherapy, taxanes, the synergistic XT combination of capecitabine and docetaxel, and other combination regimens. The neoadjuvant setting is also being utilized to evaluate new systemic agents and predictors of tumor response, including DNA microarray analysis. At this meeting, Bear and colleagues will present updated results of NSABP-B-27 evaluating sequential neoadjuvant therapy with AC → docetaxel.

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 → surgery
ARM 2	AC x 4 → T x 4 → surgery
ARM 3	AC x 4 → surgery → T x 4

AC = doxorubicin/cyclophosphamide; T = docetaxel
Patients undergoing breast-conserving surgery received radiation therapy.

SOURCE: NSABP website, September 2004.

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

	AC	AC → T	*p*-value
Lumpectomy	61.6%	63.7%	0.33
Pathologic CR	13.7%	26.1%	0.001
Node-negative	50.8%	58.2%	0.001
Deaths	0.1%	0.4%	—
Grade 4 toxicity	10.3%	23.4%	—

SOURCES: NSABP presentation. San Antonio Breast Cancer Symposium, 2001. Bear H et al. *J Clin Oncol* 2003;21(22):4165-74.

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

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

Eligibility	Inflammatory or locally advanced breast cancer Stage IIB or IIIA/B
ARM 1	AC q3wk x 5 → T qwk x 12 → surgery
ARM 2	[A qwk + Co qd + G-CSF] x 15 → T qwk x 12 → 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 Ellis, MD, Chair
Southwest Oncology Group
Tel: 206-288-6711

SOURCE: NCI Physician Data Query, October 2004.

PROPOSED NSABP-B-27R PREOPERATIVE CHEMOTHERAPY REPLACEMENT TRIAL

AC q3wk ↔ docetaxel q3wk → surgery
AC q3wk ↔ docetaxel/capecitabine q3wk → surgery
AC q3wk ↔ docetaxel/gemcitabine q3wk → surgery

In this proposed 3 x 2 factorial design, some patients will receive AC followed by docetaxel or docetaxel combination regimens; in others, the sequence of administration will be reversed.

SOURCE: NSABP website, June 2004.

MD ANDERSON PHASE III NEOADJUVANT TRIAL OF WEEKLY PACLITAXEL VERSUS CAPECITABINE/DOCETAXEL FOLLOWED BY FEC AND LOCAL THERAPY

Protocol ID: ID01-580, NCT00050167
Projected Accrual: 930 (Open)

Eligibility	Stage IIA-IIIA breast cancer
ARM 1	Paclitaxel qwk x 12 → FEC x 4 → local therapy (surgery or RT)
ARM 2	(Capecitabine + docetaxel) x 4 → FEC x 4 → local therapy (surgery or RT)

Note: ER/PR-positive patients will receive endocrine therapy after completion of local therapy.

Study Contacts:
Debbie Frye, RN; Cynthia Carter, RN
MD Anderson Cancer Center
Tel: 713-792-2817

SOURCE: NCI Physicans Data Query, October 2004.

PATHOLOGIC COMPLETE RESPONSE IN RECENTLY COMPLETED COMPARATIVE CLINICAL TRIALS OF NEOADJUVANT CHEMOTHERAPY

Study	No. of evaluable patients (OR)	Therapy	pCR	OR
NSABP-B-27[1]	752[4] 1,534[4]	AC x 4 → docetaxel x 4 AC x 4	26% 14%	91% 86%
Aberdeen Trial[2]	 52 52	CVAP x 4 Responders randomized → CVAP x 4 → docetaxel x 4	 15% 31%	66% 64% 85%
MD Anderson[3]	 50 68 51 67	Paclitaxel qwk → FAC Node-positive Node-negative Paclitaxel q3wk → FAC Node-positive Node-negative	 28% 29% 14% 13%	 NA NA NA NA

pCR = pathological complete response;
OR = objective response (complete + partial clinical response)

SOURCES: [1] Bear H et al. *J Clin Oncol* 2003;21(22):4165-74.

[2] At a median follow-up of 65 months, the survival rates were 93% in the docetaxel group versus 78% in the CVAP group ($p = 0.04$).
Hutcheon AW et al. Presentation. San Antonio Breast Cancer Symposium, 2003. *Breast Cancer Res Treat* 2003;Abstract 6.

[3] Green MC et al. *Proc ASCO* 2002;Abstract 135.

[4] These numbers reflect pCR; number of evaluable patients for OR is 722 for AC → T and 1,534 for AC.

SELECT PUBLICATIONS

Bear HD 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* 2003;21(22):4165-74**.**

Chollet P et al. **Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer.** *Br J Cancer* 2002;86(7):1041-6.

Green MC et al. **Weekly (wkly) paclitaxel (P) followed by FAC as primary systemic chemotherapy (PSC) of operable breast cancer improves pathologic complete remission (pCR) rates when compared to every 3-week (Q 3 wk) P therapy (tx) followed by FAC final results of a prospective phase III randomized trial.** *Proc ASCO* 2002;Abstract 135.

Hutcheon AW et al. **Docetaxel primary chemotherapy in breast cancer: A five year update of the Aberdeen trial.** *Breast Cancer Res Treat* 2003;Abstract 11.

Kaufmann M et al. **International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: Review and recommendations.** *J Clin Oncol* 2003;21:2600-8.

Pusztai L et al. **Emerging science: Prospective validation of gene expression profiling based prediction of complete pathologic response to neoadjuvant paclitaxel/FAC chemotherapy in breast cancer.** *Proc ASCO* 2003;Abstract 1.

Rajan R et al. **Pathologic changes in breast cancer following neoadjuvant chemotherapy: Implications for the assessment of response.** *Clin Breast Cancer* 2004;5(3):235-8.

Thomas E et al. **The use of alternate, non-cross-resistant adjuvant chemotherapy on the basis of pathologic response to a neoadjuvant doxorubicin-based regimen in women with operable breast cancer: Long-term results from a prospective randomized trial.** *J Clin Oncol* 2004;22(12):2294-302.

PREDICTING PATHOLOGIC RESPONSE TO NEOADJUVANT CHEMOTHERAPY BASED ON GENETIC PROFILING

In NSABP-B-27, all patients received AC and were randomly assigned to one of three arms: surgery, surgery followed by docetaxel, or docetaxel followed by surgery. The question is whether we can identify patients whose response to AC alone is sufficient and their risk is too low to warrant further adjuvant chemotherapy. Perhaps we can identify patients resistant to all therapies, in which case further chemotherapy is not indicated.

Lajos Pusztai and his colleagues reported a preliminary study suggesting they could identify patients most likely to have a complete pathologic response to combination chemotherapy based on gene expression profiling. Similarly, two or three other studies, including work conducted at Georgetown, suggest that not only can general resistance to all chemotherapies be predicted, but resistance to single agents in neoadjuvant therapy — such as a taxane versus doxorubicin — can also be predicted.

This research is very much in its infancy, and Dr Pusztai will chair a SWOG neoadjuvant trial with fine-needle aspiration before treatment to confirm his preliminary findings. While Dr Pusztai's study evaluated combination chemotherapy, we know that cyclophosphamide, doxorubicin and 5-FU work in very different ways. Logic tells us we'll probably find that some genes are associated with resistance to all chemotherapy and other genes are specific for individual drugs. For a long time we have fantasized about being able to individualize therapy based on a patient's genes, and I believe we're beginning to develop the tools and the technology to do just that.

— Daniel F Hayes, MD

SWOG-S0012: NEOADJUVANT THERAPY IN LOCALLY ADVANCED AND INFLAMMATORY DISEASE

In the Southwest Oncology Group, we have a trial of neoadjuvant therapy for women with locally advanced and inflammatory disease, comparing intermittent AC versus AC plus G-CSF. It's a two-arm study and all patients receive paclitaxel, but I would like to see an Intergroup trial in which patients who have resectable disease are randomly assigned to a dose-dense versus a less dose-dense schedule. In other words, it's a trial asking the same basic question that we're asking in SWOG-S0221, because with an endpoint of pathologic complete response in a two-arm design, we could potentially have an answer in a couple of years while we're still completing the adjuvant study.

— Robert B Livingston, MD

NEW STRATEGIES FOR NEOADJUVANT CHEMOTHERAPY

The neoadjuvant setting is an arena in which I believe we need more research. It is not uncommon for us to see patients after preoperative therapy and surgery who have seven positive nodes and scattered tumor throughout the breast. We don't know what to do in these cases. Obviously we put patients with ER- or PR-positive tumors on endocrine therapy, but I don't think any of us believe this is going to be a great strategy.

I believe exploring agents such as capecitabine in those patients is a great idea. I also think that some types of breast cancer have very few cells in cycle kinetically — like low-grade lymphoma. We will never cure these patients with aggressive agents, but perhaps metronomic, low-dose therapy — whether it's weekly taxanes, weekly anthracyclines or capecitabine for a prolonged period of time — would treat that component of cells that aren't cycling. All of these are great options for future studies.

— Hyman B Muss, MD