Adjuvant Endocrine Therapy Trials in Premenopausal Patients

25TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM 10

The International Breast Cancer Overview has demonstrated that adjuvant ovarian ablation significantly reduces mortality in premenopausal women, and tamoxifen reduces mortality in both pre- and postmenopausal women with ER-positive tumors. Current clinical trials are addressing a number of important issues related to these two key interventions, including the impact of combining these therapies with chemotherapy. New trials are also combining aromatase inhibitors and ovarian suppression in premenopausal women, particularly in light of the recent ATAC trial data demonstrating an advantage to anastrozole in postmenopausal women.

PHASE III RANDOMIZED COMPARISON OF ADJUVANT THERAPIES IN PREMENOPAUSAL WOMEN WITH RESECTED NODE-POSITIVE HORMONE RECEPTOR-POSITIVE ADENOCARCINOMA OF THE BREAST

Closed Protocol

Protocol IDs: INT-0101, CLB-9192, EST-5188, SWOG-8851

Projected Accrual: 1,503 eligible patients

Eligibility	Premenopausal, node-positive, hormone receptor-positive patients within 12 weeks of surgery, who received no prior endocrine or chemotherapy

ARM 1	Surgery → CAF
ARM 2	Surgery → CAF → Z x 5 years
ARM 3	Surgery → CAF → ZT x 5 years

CAF=cyclophosphamide, doxorubicin, fluorouracil; Z=goserelin; T=tamoxifen

Source: NCI Physician Data Query, November 2002.

PHASE III RANDOMIZED STUDY OF ADJUVANT TAMOXIFEN, OVARIAN SUPPRESSION AND/OR CHEMOTHERAPY IN WOMEN WITH STAGE I, II AND IIIA BREAST CANCER — Closed Protocol

Protocol IDs: CRC-TU-BR3010, EU-94029, SCTN-BR9401/BR9402, UKCCCR-ABC, YRCO-ABC

Projected Accrual: Approximately 6,000 women (4,000 premenopausal, 2,000 postmenopausal)

Eligibility	Stage I, II or IIIA breast cancer

ARM 1	Tamoxifen
ARM 2	Tamoxifen + [CMF x 6 or AC x 4]
ARM 3	Tamoxifen + ovarian suppression
ARM 4	Tamoxifen + ovarian suppression + [CMF x 6 or AC x 4]

Postmenopausal women are randomized to arms 1 or 2.

Randomization for pre- and perimenopausal women is based on the clinician's judgment of appropriate adjuvant therapy (chemotherapy and/or ovarian suppression). Patients may be randomized as follows: among all four groups; for chemotherapy alone; for ovarian suppression with nonrandomized assignment to chemotherapy; for chemotherapy with nonrandomized assignment to ovarian suppression.

Source: NCI Physician Data Query, November 2002.

KEY QUESTIONS IN THE MANAGEMENT OF PREMENOPAUSAL PATIENTS WITH ER/PR-POSITIVE TUMORS

- Importance of amenorrhea as a determinant of therapy
- Optimal duration of ovarian ablation if an LHRH analogue is used
- Value of ovarian ablation after chemotherapy, particularly for women who remain premenopausal after adjuvant chemotherapy
- Utility of combined hormone therapy such as ovarian ablation with tamoxifen, or aromatase inhibitors
- Long-term side effects of ovarian suppression

INT-0101 TRIAL RESULTS: 7.4 YEARS FOLLOW-UP

	DFS	Survival	DFS <40 yrs old
CAF	58%	77%	49%
CAFZ	64%	78%	59%
CAFZT	73%	80%	59%

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

PLANNED OR ONGOING TRIALS OF ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL PATIENTS

Study	Entry	Intervention	Target Accrual	Status
ABCSG AU12	Stage I, II	Tamoxifen + goserelin ± Zoledronate Anastrozole + goserelin ± Zoledronate	1,250	600 patients ongoing
IBCSG TEXT	T1-T3, pN0-N2	Ovarian suppression + Exemestane Ovarian suppression + Tamoxifen	2,025	Planned
IBCSG SOFT	T1-T3, pN0-N2	Tamoxifen Ovarian suppression + Tamoxifen Ovarian suppression + Exemestane	2,700	Planned

DERIVED FROM: **ASCO Technology Assessments: Aromatase inhibitors as adjuvant therapy for women with hormone receptor positive breast cancer.**

SELECT PUBLICATIONS

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Davidson N et al. **Effect of chemohormonal therapy in premenopausal, node (+), receptor (+) breast cancer: An Eastern Cooperative Oncology Group phase III Intergroup trial (E5188, INT-0101).** *Proc ASCO* 1999; Abstract 249A, 67A.

Gnant M et al. **Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: Results of a randomized multicenter trial.** *Breast Cancer Res Treat* 2002; Abstract 450.

Henderson IC. **Ovarian ablation comes around again.** *Breast Diseases: A Year Book Quarterly* 2000;11(2):117-120.

Klijn JG et al. **Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: A meta-analysis of four randomized trials.** *J Clin Oncol* 2001;19:343-353.

Michaud LB, Buzdar AU. **Complete estrogen blockade for the treatment of metastatic and early stage breast cancer.** *Drugs Aging* 2000;16:261-271.

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INTERGROUP 0101 STUDY OF ADJUVANT OVARIAN ABLATION

In the best of all worlds, we would have had a fourth arm of CAF followed by tamoxifen. At the time, however, we weren't sure that we could accrue to that trial in a timely fashion and have something to talk about. The disease-free survival was better for the group receiving CAFZT compared to CAFZ. There was a borderline improvement with CAFZ compared to CAF. An unplanned, retrospective subset analysis demonstrated that younger women — arbitrarily defined as under age 40 — seemed to do better with goserelin. Perhaps that's not surprising, because those women are the least likely to be made postmenopausal by chemotherapy. There's also a suggestion that women with premenopausal estrogen levels after chemotherapy were destined to derive benefit from goserelin. The big clinical question now is what to do with the young woman who is premenopausal at the end of chemotherapy.

—Nancy E Davidson, MD

ADJUVANT OVARIAN ABLATION IN A NONPROTOCOL SETTING

In the ECOG study, patients received CAF, which everyone would consider state-of-the-art chemotherapy. In that trial, there was additional benefit from adding ovarian ablation to CAF — certainly among women under age 40. That study really changed my thinking. If a woman with an ER-positive cancer receives adjuvant chemotherapy and does not stop menstruating, I routinely add an LHRH agonist with tamoxifen.

—I Craig Henderson, MD

LHRH AGONISTS PLUS TAMOXIFEN

Combination endocrine therapy is a conceptual change for us. We eliminated that approach a couple of decades ago, perhaps because of small, inadequately powered trials that were clearly unable to detect the type of differences we can identify today with larger studies. With better research tools now available, we are returning to the concept of complete estrogen blockade — a strategy that started several decades ago with hypophysectomy and adrenalectomy.

—Gabriel Hortobagyi, MD

AROMATASE INHIBITORS IN WOMEN MADE MENOPAUSAL BY LHRH AGONISTS

There is one limited metastatic study in ER-positive patients demonstrating that goserelin plus anastrozole yielded similar responses to what has been seen with aromatase inhibitors in postmenopausal patients, but we need to design appropriate trials to address this issue. It is very important to consider that aromatase inhibitors as monotherapy should not be used in premenopausal patients. But it would be a very interesting and logical approach to design trials of complete estrogen blockade in ER-positive premenopausal patients using an LHRH agonist and an aromatase inhibitor.

—Aman Buzdar, MD

ADJUVANT TRIALS ON THE HORIZON

One-third of breast cancer cases occur in premenopausal women. LHRH agonists are as effective as chemotherapy in women with ER-positive tumors. LHRH agonists render a woman postmenopausal, and that poses an interesting research question: Should we be using LHRH agonists plus an aromatase inhibitor as a more complete method to deprive tumors of estrogen?

— Jack Cuzick, PhD