Adjuvant Endocrine Therapy in Premenopausal Patients

Adjuvant tamoxifen has an established role in premenopausal women with ER-positive breast cancer. With a median follow-up of 9.6 years, INT 0101 demonstrated that the addition of tamoxifen to CAF plus goserelin improved the time to recurrence and disease-free survival. However, no benefits were associated with CAF plus goserelin compared to CAF alone, although the analysis was confounded by the fact that most of the premenopausal women in the study experienced ovarian ablation from chemotherapy, and a subset analysis demonstrated a benefit of goserelin in patients who continued to menstruate after chemotherapy. Ongoing clinical trials — SOFT and TEXT — are evaluating the role of ovarian ablation/suppression combined with either tamoxifen or an aromatase inhibitor. An Austrian study — ABCSG-AU12 — reported by Dr Michael Gnant at the 2004 San Antonio Breast Cancer Symposium demonstrated that zoledronate counteracted the bone loss associated with both goserelin/tamoxifen and goserelin/anastrozole. Results from ongoing trials will help establish the optimal adjuvant hormonal therapy for premenopausal women.

TRIALS OF ADJUVANT ENDOCRINE THERAPY WITH OVARIAN SUPPRESSION

Study	N	Eligibility	Randomization
IBCSG-24-02 (SOFT trial)	3,000 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Tamoxifen x 5y OFS + tamoxifen x 5y OFS + exemestane x 5y
IBCSG-25-02 (TEXT trial)	1,845 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Triptorelin ± chemotherapy + tamoxifen x 5y Triptorelin ± chemotherapy + exemestane x 5y
IBCSG-26-02 (PERCHE* trial)	1,750 (Closed)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	OFS + tamoxifen or exemestane x 5y OFS + any chemotherapy + tamoxifen or exemestane x 5y

OFS = ovarian function suppression with triptorelin or surgical oophorectomy or ovarian irradiation
* The PERCHE trial has closed. Accrual as of December 16, 2005 = 15/1,750.

SOURCES: www.ibcsg.org; NCI Physician Data Query, January 2006.

PHASE III STUDY COMPARING AN LHRH AGONIST WITH TAMOXIFEN OR ANASTROZOLE WITH OR WITHOUT ZOLEDRONATE

Protocol ID: ABCSG-AU12
Target Accrual: 1,800 (Open)

Eligibility	Premenopausal women with hormone-responsive breast cancer, Stages I/II
ARM 1	Tamoxifen + goserelin
ARM 2	Anastrozole + goserelin
ARM 3	Tamoxifen + goserelin + zoledronate
ARM 4	Anastrozole + goserelin + zoledronate

SOURCE: Gnant M et al. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 6.

RANDOMIZED TRIAL OF CHEMOHORMONAL THERAPY IN PREMENOPAUSAL, NODE-POSITIVE, RECEPTOR-POSITIVE BREAST CANCER (INT 0101)

Protocol ID: INT 0101, E5188
Accrual: 1,503 (Closed)

Eligibility	Premenopausal patients with node-positive, hormone receptor-positive breast cancer
ARM 1	CAF x 6
ARM 2	CAF x 6 → Z x 5y
ARM 3	CAF x 6 → ZT x 5y

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

SOURCE: Davidson N et al. *J Clin Oncol* 2005;23(25):5973-82.

INT 0101 TRIAL RESULTS: 9.6 YEARS' FOLLOW-UP

	CAF (n = 494)	CAF-Z (n = 502)	CAF-ZT (n = 507)	Hazard ratio (HR)* (CAF-Z/CAF)	Hazard ratio (HR)* (CAF-ZT/CAF-Z)
Nine-year disease-free survival	57%	60%	68%	0.90 ($p = 0.15$)	0.74 ($p < 0.01$)
Nine-year overall survival	70%	73%	76%	0.86 ($p = 0.10$)	0.91 ($p = 0.23$)
Nine-year time to recurrence	58%	61%	68%	0.91 ($p = 0.17$)	0.73 ($p < 0.01$)

CAF = cyclophosphamide, doxorubicin and fluorouracil; Z = goserelin; T = tamoxifen
* HR adjusted for age, nodal and ER/PR status; p is one sided (compared with $\propto = 0.025$).

SOURCE: Davidson N et al. *J Clin Oncol* 2005;23(25):5973-82.

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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 12.

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INT 0101 (E5188) TRIAL

A major strength is that trial eligibility was defined by a physiological definition for the premenopausal state, rather than age, as truly premenopausal women are most likely to benefit from such an approach. Further, participation was restricted to patients with an ER- and/or PR-positive tumor — the subset of women most likely to benefit from endocrine therapy. …

E5188 provides the most extensive information to date about the utility of chemoendocrine therapy in premenopausal women with node-positive, receptor-positive breast cancer. The findings from this study clearly support the use of tamoxifen after chemotherapy for premenopausal, node-positive, receptor-positive breast cancer. …

— Nancy E Davidson, MD et al.
J Clin Oncol *2005;23(25):5973-82.*

AROMATASE INHIBITOR USE IN PREMENOPAUSAL WOMEN

The data are quite convincing that the aromatase inhibitors should play a role as adjuvant hormonal therapy for postmenopausal women with ER-positive breast cancer. Precisely how to sequence or to incorporate those data into the premenopausal subset is much less clear. We do know that the aromatase inhibitors do not suppress circulating estrogen levels adequately in women with functioning ovaries, whether or not they have menstrual function. Therefore, if you're going to use an AI for a young woman, you have to be certain that she is postmenopausal, or I think she should be enrolled in one of the prospective trials evaluating the use of ovarian suppression and an aromatase inhibitor in premenopausal women.

We do know that a number of women stop having menstrual function or periods subsequent to cytotoxic chemotherapy, yet their ovaries continue to cycle. A substantial proportion of women also stop having ovarian function with cytotoxic chemotherapy, at least over the short term, but on further follow-up, their ovarian function returns.

— Robert W Carlson, MD.
Meet The Professors *2005 (3)*

The ABCSG-AU12 trial randomly assigned approximately 2,000 patients to goserelin plus tamoxifen versus goserelin plus anastrozole, with a second randomization to zoledronic acid or not. That study will report in one or two years and should tell us whether tamoxifen or an aromatase inhibitor is superior when combined with goserelin in premenopausal women. We expect that goserelin with anastrozole will be better, which is why so many patients are already being treated off protocol.

— Anthony Howell, MD.
Breast Cancer Update *2005 (4)*

Tamoxifen remains the mainstay of treatment for premenopausal patients. Certainly, in Europe there is a very strong feeling that the published data seem to indicate that the addition of ovarian ablation to tamoxifen is superior to either of those modalities alone. In Europe, it's very hard to convince the vast majority of oncologists that the question of treatment approach in these patients has not already been answered.

However, the fact that we have the SOFT, TEXT and PERCHE* trials examining this very issue indicates that, at least in the minds of most North American oncologists, the question remains unanswered as to the best adjuvant therapy for premenopausal patients. The answers are not in and won't be in for many years. In the meantime, oncologists are stuck deciding what to do.

Do you or don't you believe that the addition of ovarian ablation adds to orally administered hormonal therapy? Certainly, you cannot use an aromatase inhibitor in premenopausal patients and expect it to work unless you render them postmenopausal.

* The PERCHE trial has closed. Accrual as of December 16, 2005 = 15/1,750.

— Charles L Vogel, MD.
Breast Cancer Update *2005 (9)*