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 achieved ovarian ablation from chemotherapy, and a subset analysis demonstrated a benefit in patients who continued to menstruate after chemotherapy. Ongoing clinical trials — SOFT, TEXT and PERCHE — 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 hopefully 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 (Open)	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

SOURCES: www.ibcsg.org; NCI Physician Data Query, September 2005.

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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Love RR et al. **Her-2/neu overexpression and response to oophorectomy plus tamoxifen adjuvant therapy in estrogen receptor-positive premenopausal women with operable breast cancer.** *J Clin Oncol* 2003;21(3):453-7.

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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 today 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)

Cessation of menses does not necessarily mean absence of ovarian function, as premenopausal estradiol levels may be found in women experiencing chemotherapy-related amenorrhea. There is widespread agreement that aromatase inhibitors should not be employed as monotherapy in premenopausal women. This view stems from the lack of evidence for adequate estrogen suppression and potential for stimulation of the ovaries via increased gonadotropin release.

— 2004 ASCO Technology Report on Use of Aromatase Inhibitors as Adjuvant Therapy

We were particularly interested in younger patients because they are physiologically used to higher levels of estrogen from their functioning ovaries. We undertook ABCSG-12 to first establish the severity of that treatment-induced bone loss and, second, whether it can be prevented or treated. We found out that a significant loss occurs — on average close to 15 percent — in these premenopausal women treated with endocrine therapy. We also discovered that it could be prevented with zoledronic acid given twice a year.

— Michael Gnant, MD.* Breast Cancer Update *2005 (4)

Three important randomized trials are enrolling premenopausal women with hormone-receptive disease — SOFT, TEXT and PERCHE. 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)