Adjuvant Endocrine Therapy in Premenopausal Patients

Tamoxifen has an established role as adjuvant systemic therapy for premenopausal women with estrogen receptor-positive breast cancer. A number of major current clinical trials are evaluating the role of ovarian ablation/suppression combined with either tamoxifen or an aromatase inhibitor. A related and important issue is the impact of chemotherapy-related ovarian suppression in these patients. While it will be many years before data on disease-free and overall survival are available from these studies, an Austrian study reported by Gnant at the San Antonio Breast Cancer Symposium in 2002 and 2004 demonstrated that bone loss associated with ovarian suppression combined with either tamoxifen or anastrozole can largely be avoided by the use of the bisphosphonate zoledronate.

RANDOMIZED ADJUVANT TRIAL OF TAMOXIFEN AND GOSERELIN VERSUS CYCLOPHOSPHAMIDE, METHOTREXATE AND FLUOROURACIL IN PREMENOPAUSAL PATIENTS

Protocol ID: ABCSG-05
Accrual: 1,034 (Closed)

Eligibility	Patients with Stage I or II ER/PR-positive breast cancer
ARM 1	Surgery + RT → goserelin q28d x 3y + tamoxifen x 5y
ARM 2	Surgery + RT → CMF on days 1, 8 q28d

ABCSG-05 TRIAL RESULTS: FIVE-YEAR FOLLOW-UP

	Goserelin + tamoxifen (n=511)	CMF (n=523)	*p*-value
Breast cancer-specific deaths	41 (8%)	51 (10%)	0.900
Relapses	88 (17%)	109 (21%)	0.0176
Local recurrences	24 (5%)	42 (8%)	0.0029
Cancer in opposite breast	3 (1%)	12 (3%)	0.0001

RT = radiation therapy

Although the data for survival are less mature than for relapse-free survival, the hazard ratio estimate for overall survival favored endocrine therapy ($p = 0.195$).

SOURCSE: Gnant M. Presentation. San Antonio Breast Cancer Symposium, 2002.

Jakesz R et al. *J Clin Oncol* 2002;20(24):4621-7.

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. Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 6.

SOFT: SUPPRESSION OF OVARIAN FUNCTION TRIAL

Protocol ID: IBCSG 24-02
Target Accrual: 3,000 (Open)

Eligibility	Premenopausal; estradiol (E_2) in the premenopausal range after or without chemotherapy; ER ≥10% and/or PgR ≥10%
ARM 1	Tamoxifen x 5y
ARM 2	OFS + tamoxifen x 5y
ARM 3	OFS + exemestane x 5y

OFS = ovarian function suppression using triptorelin for five years or surgical oophorectomy or ovarian irradiation

SOURCE: www.ibcsg.org

TEXT: TAMOXIFEN AND EXEMESTANE TRIAL

Protocol ID: IBCSG 25-02
Target Accrual: 1,845 (Open)

Eligibility	ER ≥10% and/or PgR ≥10%; candidates to begin GnRH analogue from the start of adjuvant therapy
ARM 1	GnRH ± chemotherapy + tamoxifen x 5y
ARM 2	GnRH ± chemotherapy + exemestane x 5y

GnRH = triptorelin for five years, but oophorectomy or ovarian irradiation is allowed after six months

SOURCE: www.ibcsg.org

PERCHE: PREMENOPAUSAL ENDOCRINE RESPONSIVE CHEMOTHERAPY TRIAL

Protocol ID: IBCSG 26-02
Target Accrual: 1,750 (Open)

Eligibility	Premenopausal women with ER ≥10% and/or PgR ≥10%; patients for whom chemotherapy is considered to be a randomized option (lower risk)
ARM 1	OFS + T or E x 5y
ARM 2	OFS + T or E x 5y + any chemotherapy

OFS = ovarian function suppression using triptorelin or surgical oophorectomy or radiation; T = tamoxifen; E = exemestane

SOURCE: www.ibcsg.org

SELECT PUBLICATIONS

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Davidson N et al. **Chemohormonal therapy in premenopausal node-positive receptor-positive breast cancer: An Eastern Cooperative Oncology Group Phase III Intergroup trial (E5188, INT-0101).** *Proc ASCO* 2003;Abstract 15.

de Haes H et al. **Quality of life in goserelin-treated versus cyclophosphamide + methotrexate + fluorouracil-treated premenopausal and perimenopausal patients with node-positive, early breast cancer: The Zoladex Early Breast Cancer Research Association Trialists Group.** *J Clin Oncol* 2003;21(24):4510-6.

Early Breast Cancer Trialists' Collaborative Group. **Ovarian ablation for early breast cancer.** *Cochrane Database Syst Rev* 2000;CD000485.

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Jakesz R et al; Austrian Breast and Colorectal Cancer Study Group Trial 5. **Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: Evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer — Austrian Breast and Colorectal Cancer Study Group Trial 5.** *J Clin Oncol* 2002;20(24):4621-7.

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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.

Love RR et al. **Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnamese and Chinese women with operable breast cancer.** *J Clin Oncol* 2002;20(10):2559-66.

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OVARIAN SUPPRESSION IN THE TREATMENT OF PREMENOPAUSAL WOMEN

The IBCSG is coordinating a series of three nested trials: SOFT, PERCHE and TEXT. These trials address what is probably the most important conceptual question in premenopausal breast cancer right now: Beyond tamoxifen, does planned ovarian suppression benefit patients?

In particular, does it benefit women who receive chemotherapy or who don't receive chemotherapy, and if a woman experiences chemotherapy-related amenorrhea, does she still need ovarian suppression? We probably won't have the data for at least five or 10 years, but these are very important trials in which community oncologists can participate to answer these critical questions.

Currently, I consider ovarian suppression for two groups of patients. The first group consists of patients at high risk — multiple positive nodes, high-risk tumors — and women less than 35 or 40 years of age who may not go into menopause with chemotherapy. The other group includes women who are at the opposite end of the spectrum — low-risk tumors, smaller tumors, node-negative — for whom the benefits of chemotherapy are small. For these women, I present ovarian suppression as an option, not necessarily in addition to chemotherapy but perhaps even instead of it.

— Harold J Burstein, MD, PhD

For premenopausal women with node-positive, ER-positive disease, I use tamoxifen and chemotherapy. While the standard of care is tamoxifen, you wouldn't be wrong to give goserelin followed by tamoxifen or anastrozole; however, I don't use goserelin because of the menopausal symptoms. Until we see the study data, I am not comfortable using an aromatase inhibitor with an LHRH agonist. I prefer using aromatase inhibitors in women who undergo a prophylactic oophorectomy. A German study is comparing goserelin plus anastrozole to goserelin plus tamoxifen. They have already presented data demonstrating that bisphosphonates can eliminate the risk of osteoporosis associated with aromatase inhibitors.

— Gershon Locker, MD

ABCSG-12: LHRH AGONIST WITH TAMOXIFEN OR ANASTROZOLE WITH OR WITHOUT ZOLEDRONIC ACID

This trial is basically attempting to establish the value of aromatase inhibitors for premenopausal patients with hormone receptor-positive breast cancer. The study will also look at the severity of treatment-induced bone loss and attempt to determine whether we can prevent or treat it.

The main difference between ABCSG-12 and the SOFT and TEXT trials is that cytostatic chemotherapy is only allowed in our trial as neoadjuvant therapy. This may be criticized, but we have previously established that at least some of these patients can be treated without chemotherapy and, clearly, this has an advantage in terms of avoiding toxicity. Eighty percent of patients on this trial have node-negative disease.

The bone substudy for ABCSG-12 closed 18 months ago and we now have results from 401 patients. We presented similar data two years ago that were criticized for being too early. These current data are far more mature and the results are beyond any doubt. Unlike the postmenopausal setting where we know that tamoxifen protects bone via estrogenic agonistic effects, in the premenopausal setting tamoxifen is not able to balance the impact of ovarian suppression. In this study, we observed 11 percent bone loss when goserelin plus tamoxifen was used. At least 40 percent more bone loss occurred with an aromatase inhibitor in the same situation.

The other important piece of data from this trial indicates that the bone loss from hormonal therapy can be prevented with the application of zoledronic acid twice a year. Absolutely no difference between baseline bone density and the 36-month measurements occurred in the two groups treated with the bisphosphonate.

— Michael Gnant, MD