Neoadjuvant Endocrine Therapy

Chemotherapy is the most frequent form of neoadjuvant systemic therapy utilized in the United States; in Europe, preoperative endocrine therapy has been used extensively in women with ER-positive cancers. Phase II and III clinical trials have suggested that the antitumor effect of endocrine therapy in these patients is comparable to what has been observed with chemotherapy, although the time to achieve a response may be somewhat longer. Tamoxifen and ovarian ablation/suppression were initially utilized in neoadjuvant studies, and more recently, third-generation aromatase inhibitors and the estrogen receptor downregulator fulvestrant have demonstrated significant antitumor activity in this setting. At last year's San Antonio Breast Cancer Symposium, data were presented from the IMPACT trial comparing anastrozole, tamoxifen and the combination. As was observed in a previous trial comparing letrozole to tamoxifen, breast-conserving surgery was much more common in women treated with anastrozole than in women treated with tamoxifen.

IMPACT TRIAL: A RANDOMIZED DOUBLE-BLIND TRIAL OF PREOPERATIVE TAMOXIFEN, ANASTROZOLE OR THE COMBINATION IN POSTMENOPAUSAL BREAST CANCER PATIENTS

Eligibility	Postmenopausal, ER/PR-positive T2 (≥2 cm), T3, T4b N0-2, M0 breast cancer patients
ARM 1	Tamoxifen x 3 months → surgery
ARM 2	Anastrozole x 3 months → surgery
ARM 3	Anastrozole + tamoxifen x 3 months → surgery

SOURCE: Smith I, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003;Abstract 1.

ANASTROZOLE (A) VERSUS TAMOXIFEN (T) VERSUS THE COMBINATION (C) AS NEOADJUVANT ENDOCRINE THERAPY FOR POSTMENOPAUSAL PATIENTS WITH ESTROGEN RECEPTOR-POSITIVE BREAST CANCER: THE IMPACT TRIAL (N=330)

	A	T	C
Objective clinical tumor response[1]	37.2%	36.1%	39.4%
Patients who became eligible for breast-conserving surgery* after 3 months of treatment[1]	45.7%	22.2%	26.2%
Geometric mean reductions in Ki67 after 2 weeks of treatment[2]**	76%	59%	64%

* Of the 220 patients with surgeon's preferred surgery recorded at baseline, 56% were deemed to need a mastectomy.

** Reductions in Ki67 were virtually maximal at 2 weeks with only marginal changes between 2 and 12 weeks.

SOURCES: [1] Smith I, Dowsett M, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003:Abstract 1.

[2] Dowsett M, Smith I, on behalf of the IMPACT Trialists. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;Abstract 2.

RESPONSE RATES FOLLOWING NEOADJUVANT ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH LOCALLY ADVANCED BREAST CANCER

Clinical response (n=74)	Response rate
Complete clinical response (cCR)	57%
Partial clinical response (cPR)	26%
Objective response (cCR + cPR)	83%
Pathological response (n=61)*	**Response rate**
Complete pathologic response (pCR)	23%
Partial pathologic response (pPR)	77%

* Pathological response data limited to patients showing an objective response who then underwent a mastectomy

SOURCE: Milla-Santos A et al. **Anastrozole as neoadjuvant therapy for patient with hormone-dependent, locally-advanced breast cancer.** *Anticancer Research* 2004;24:1315-8.

ANASTROZOLE (A) VERSUS TAMOXIFEN (T) VERSUS COMBINED (A+T) AS NEOADJUVANT ENDOCRINE THERAPY FOR POSTMENOPAUSAL BREAST CANCER PATIENTS (N=87)

	A	T	A+T	*p*-value
Overall objective response (clinical)	70%	44.4%	49%	0.048
Mammographic response	56%	36%	40%	0.058
Ultrasound response	44%	30%	32%	0.072
Breast-conserving surgery	42%	28%	30%	0.056

DERIVED FROM: Semiglazov V et al. **Anastrozole (A) versus tamoxifen (T) versus combination (A+T) as neoadjuvant endocrine therapy of postmenopausal breast cancer patients.** *Proc ASCO* 2003;Abstract 3538.

RESPONSE DATA COMPARING NEOADJUVANT LETROZOLE TO TAMOXIFEN IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE BREAST CANCER

Therapy	n	Overall response	Underwent successful breast-conserving surgery*	*p*-value
Letrozole	124	60%	48%	0.004
Tamoxifen	126	41%	36%	0.036

* At baseline, all tumors were considered not amenable to breast-conserving surgery.

SOURCE: Ellis MJ. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a Phase III randomized trial.** *J Clin Oncol* 2001;19(18):3808-16.

EFFICACY OF FOUR TO EIGHT MONTHS OF DAILY PREOPERATIVE LETROZOLE IN POSTMENOPAUSAL WOMEN WITH ER/PGR-POSITIVE BREAST CANCER (N=33)

Complete or partial response based on length of therapy	
Up to 4 months	57%
Longer than 4 months	90%

SOURCE: Paepke S et al. **A multi-center study of pre-operative treatment with letrozole for optimal duration of treatment in postmenopausal women with ER and/or PGR positive breast cancer.** *Proc ASCO* 2003;Abstract 321.

SELECT PUBLICATIONS

Dalenc F et al. **Tamoxifen and exemestane (E) in combination as neoadjuvant treatment of hormone sensitive post-menopausal breast cancer women: Clinical efficacy and effects on tumor pathology and immunopathology.** *Proc ASCO* 2004;Abstract 9666.

Dixon JM. **Role of endocrine therapy in the neoadjuvant surgical setting.** *Ann Surg Oncol* 2004;11(1 Suppl):18-23.

Dowsett M, on behalf of the IMPACT Trialists, Royal Marsiden Hospital, London, United Kingdom. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;Abstract 2.

Dowsett M et al. **Molecular effects of anastrozole (A) and tamoxifen (T) alone and combined (C) in the IMPACT trial of neoadjuvant treatment of primary breast cancer.** *Proc ASCO* 2004;Abstract 537.

Ellis MJ et al. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial.** *J Clin Oncol* 2001;19(18):3808-16.

Ellis MJ. **Neoadjuvant endocrine therapy as a drug development strategy.** *Clin Cancer Res* 2004;10(1 Pt 2):391S-5S.

Milla-Santos A et al. **Anastrozole as neoadjuvant therapy for patient with hormone-dependent, locally-advanced breast cancer.** *Anticancer Research* 2004;24:1315-8.

Paepke S et al. **A multi-center study of pre-operative treatment with letrozole for optimal duration of treatment in postmenopausal women with ER and/or PGR positive breast cancer.** *Proc ASCO* 2003;Abstract 321.

Semiglazov V et al. **Anastrozole (A) vs tamoxifen (T) vs combination (A+T) as neoadjuvant endocrine therapy of postmenopausal breast cancer patients.** *Proc ASCO* 2003;Abstract 3538.

Semiglazov VF et al. **The relative efficacy of neoadjuvant endocrine therapy vs chemotherapy in postmenopausal women with ER- positive breast cancer.** *Proc ASCO* 2004;Abstract 519.

Smith I, on behalf of the IMPACT Trialists, Royal Marsden Hospital, London, United Kingdom. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003;Abstract 1.

Wong ZW, Ellis MJ. **Neoadjuvant endocrine therapy for breast cancer: an overlooked option?** *Oncology (Huntingt)* 2004;18(4):411-20.

IMPACT NEOADJUVANT TRIAL

The IMPACT trial compared anastrozole, tamoxifen and a combination of the two as neoadjuvant therapy in postmenopausal women with ER-positive tumors more than two centimeters. In the intent-to-treat analysis for clinical response, no difference was found between anastrozole, tamoxifen and the combination. However, in women requiring mastectomy at baseline, anastrozole demonstrated a significant advantage over tamoxifen in terms of rendering the women eligible for breast-conserving surgery — between 40 and 50 percent of the women in the anastrozole arm and just over 20 percent in the tamoxifen arm.

In a previous neoadjuvant trial comparing an aromatase inhibitor to tamoxifen, letrozole was used. In that particular study, all of the patients required mastectomy at baseline. For some biological reason, patients requiring mastectomy seem to do better with an aromatase inhibitor than with tamoxifen. It would be interesting to find out why the aromatase inhibitors have greater antitumor effect in these larger tumors.

— Mitchell Dowsett, PhD

PREDICTING RESPONSE TO NEOADJUVANT ENDOCRINE THERAPY

Neoadjuvant chemotherapy and neoadjuvant hormonal therapy offer great potential advantages. If we can find surrogate markers to predict outcomes, we can speed up, by many years, the ability to determine which treatments work in the adjuvant setting. The investigators from the IMPACT trial were trying to make that point. In terms of reducing Ki67, anastrozole was better than tamoxifen, which parallels the ultimate outcome of the ATAC trial. I don't believe in using a single marker as the only surrogate. However, if we can use a surrogate marker to predict the ultimate outcome and correlate it with survival, then these trials may not need to enroll 3,000 to 5,000 patients. Instead, they can enroll 300 to 400 patients and provide an answer within a year. Now we need to prove that surrogates correlate with survival, and the IMPACT trial was an interesting first step in that direction.

The IMPACT trial seemed to confirm that the aromatase inhibitors might be better than tamoxifen in patients with HER2-positive disease. It could be that the benefit associated with anastrozole in the ATAC trial was largely due to the population with HER2-positive disease, and tamoxifen and anastrozole may be equally effective in patients who don't overexpress HER2. It's also possible that anastrozole is better even in the patients with HER2-negative disease. I would like to see that analysis of the ATAC trial data.

— Jeffrey Abrams, MD

NEOADJUVANT CLINICAL TRIALS OF AROMATASE INHIBITORS

We conducted a neoadjuvant trial comparing letrozole to tamoxifen in postmenopausal women with ER-positive breast cancer. Like the IMPACT trial, our study showed aromatase inhibitors to be more beneficial in favorably impacting the rates of breast-conserving surgery. The IMPACT trial had three arms whereas our trial had only two, so theirs wasn't as well powered to show a difference between just tamoxifen and an aromatase inhibitor.

In addition, the IMPACT trial allowed smaller tumors and, clinically, it's difficult to be certain you're measuring response with these smaller tumors. This might explain why their trial did not show much difference in clinical response between the arms.

We're moving ahead with an ACOSOG neoadjuvant study comparing exemestane with or without celecoxib in postmenopausal women with ER-positive, Stage II/III breast cancer who are ineligible for breast-conserving surgery or whose tumors are inoperable. In the United Kingdom, Mike Dixon is the principal investigator for a trial comparing neoadjuvant letrozole and anastrozole. I believe it's important to compare the various aromatase inhibitors because ultimately these agents will be off patent and inexpensive. Knowing which is the most efficacious will be important.

— Matthew J Ellis, MD, PhD