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 cancer. 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 the 2003 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.

IMPACT TRIAL: ANASTROZOLE VERSUS TAMOXIFEN VERSUS THE COMBINATION

Eligibility: Postmenopausal, ER/PR-positive T2 (≥2 cm), T3, T4b NO-2, MO breast cancer patients

Efficacy data (N=330)	A	T	C
Objective clinical tumor response[†]	37.2%	36.1%	39.4%
Patients who became eligible for breast-conserving surgery* after three months of treatment[†]	45.7%	22.2%	26.2%
Geometric mean reductions in Ki67 after two weeks of treatment[2‡]	76%	59%	64%

A = anastrozole; T = tamoxifen; C = combination

* 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 two weeks with only marginal changes between two 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.

‡ 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.

LETROZOLE VERSUS 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.

NEOADJUVANT ENDOCRINE THERAPY VERSUS CHEMOTHERAPY FOR POSTMENOPAUSAL PATIENTS WITH ER-POSITIVE BREAST CANCER

Response	Chemotherapy*	Anastrozole	Exemestane
Clinical objective response	76%	75.6%	81.5%
Mammographic objective response	61.9%	62.1%	71%
Qualified for breast-conserving therapy	23.9%	33.3%	34%

* Chemotherapy = doxorubicin + paclitaxel

SOURCE: Semiglazov VF et al. **Neoadjuvant endocrine therapy vs chemotherapy for postmenopausal ER-positive breast cancer patients.** *Proc SABCS* 2004;Abstract 2090.

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 pathological response (pCR)	23%
Partial pathological 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 patients with hormone-dependent, locally-advanced breast cancer.** *Anticancer* 2004;24(2C):1315-8.

ANASTROZOLE VERSUS TAMOXIFEN VERSUS THE COMBINATION AS NEOADJUVANT ENDOCRINE THERAPY FOR POSTMENOPAUSAL BREAST CANCER PATIENTS (N=87)

	A	T	A + T	*p*-value
Overall objective response (clinical)	70%	44%	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

A = anastrozole; T = tamoxifen

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.

CLINICAL RESPONSE TO NEOADJUVANT LETROZOLE

Duration of therapy	Median reduction in tumor volume	95% CI
0-3 months (n=42)	52%	37-62
3-6 months (n=42)	57%	26-100
6-12 months (n=22)	66%	22-100
Duration of therapy	**Number of complete responses**	**Percent**
3 months (n=42)	4	9.5
6 months (n=42)	12	29
12 months (n=22)	8	36

SOURCE: Renshaw L et al. **Is there an optimal duration of neoadjuvant letrozole therapy?** *Proc SABCS* 2004;Abstract 405.

SELECT PUBLICATIONS

Dixon JM et al. **Anastrozole demonstrates clinical and biological effectiveness in estrogen receptor-positive breast cancers, irrespective of the erbB2 status.** *Eur J Cancer* 2004;40(18):2742-7.

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.

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.

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.

Milla-Santos A et al. **Anastrozole as neoadjuvant therapy for patients with hormone-dependent, locally-advanced breast cancer.** *Anticancer Res* 2004;24(2C):1315-8.

Renshaw L et al. **Is there an optimal duration of neoadjuvant letrozole therapy?** *Proc SABCS* 2004;Abstract 405.

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. **Neoadjuvant endocrine therapy vs chemotherapy for postmenopausal ER-positive breast cancer patients.** *Proc SABCS* 2004;Abstract 2090.

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.

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 larger 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

I believe the IMPACT trial demonstrates the poor utility of clinical response as an endpoint in neoadjuvant trials. In many respects, reduction in tumor volume is more valuable. If reduction in tumor volume had been evaluated for the patients in the IMPACT trial, I suspect the trial would have demonstrated that anastrozole was superior, as evidenced by the fact that more patients with larger tumors had breast-conserving surgery.

For surgeons who want to shrink larger tumors and be able to perform breast-conserving surgery, it's not just response but the degree of response that is important. In our neoadjuvant studies, the reduction in tumor volume was much better with all of the aromatase inhibitors (including anastrozole) compared to tamoxifen.

— J Michael Dixon, MD

ENDOCRINE THERAPY VERSUS CHEMOTHERAPY IN THE NEOADJUVANT SETTING

With regard to neoadjuvant treatments, I believe it was a mistake to evaluate chemotherapy rather than endocrine therapy in some of the earlier animal studies. The perioperative phase is critical and while no evidence indicates that preoperative chemotherapy improves survival, that's nonspecific treatment and it doesn't mean that neoadjuvant endocrine therapies will fail. I view neoadjuvant endocrine treatment as a biological response modifier, and I believe using the aromatase inhibitors up front might have a greater impact on long-term outcome.

— Michael Baum, MD, ChM

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 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, MB, PhD