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Role of Endocrine Therapy in the Neoadjuvant Surgical Setting

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Most neoadjuvant (preoperative) therapy of breast cancer has involved the use of chemotherapy, but primary endocrine therapy has also been shown to be effective in postmenopausal women with estrogen receptor–positive tumors. Neoadjuvant therapy can reduce tumor volume, permitting surgery for otherwise inoperable tumors or allowing breast-conserving surgery rather than mastectomy for operable tumors. The preoperative treatment setting also allows for assessment and comparison of responses to different agents, which may then be used in the adjuvant therapy setting following surgery. Since tumor biopsies can be obtained before, during, and after preoperative therapy, the relationship between biomarkers and response or resistance to surgery can be investigated. In the Edinburgh Breast Unit, neoadjuvant endocrine therapy with aromatase inhibitors has been more successful than with tamoxifen. Recurrence rates following preoperative endocrine therapy and breast-conserving surgery have been acceptably low, provided that radiation therapy was also administered postoperatively. Both the probability of response to neoadjuvant letrozole or tamoxifen and the degree of tumor shrinkage increased as estrogen receptor expression increased, consistent with the results of other studies. Attempts to identify biomarkers of response to neoadjuvant endocrine therapy are under way, with early indications that reduced cell proliferation 14 days after initiation of treatment correlates with responses to tamoxifen.

Key Words: Letrozole—Tamoxifen—Biomarkers—Breast-conserving surgery

Locally advanced (stage III) breast cancer accounts for nearly 70% of all cases of breast cancer worldwide.[1] When these patients are ineligible for surgery because of large tumor size or disease extent, neoadjuvant (preoperative or primary) systemic chemotherapy often achieves sufficient tumor shrinkage to permit successful local therapy with surgery and/or radiotherapy. As an extension of this approach, neoadjuvant chemotherapy can also be used for patients with large but operable breast cancers, to enable breast-conserving surgery in cases that would otherwise require mastectomy. Clinical outcome is not worse as a consequence of neoadjuvant therapy, since disease-free survival and overall survival are not significantly different among patients who received preoperative versus postoperative chemotherapy.[2,3]

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Although neoadjuvant therapy of breast cancer has, until recently, largely been limited to chemotherapy, endocrine treatment is becoming an increasingly reasonable alternative in postmenopausal women with hormone receptor–positive tumors who may not tolerate the toxicities associated with chemotherapy.[4] Unfortunately, until recently there have been few controlled studies of neoadjuvant endocrine or chemoendocrine therapy, and in some of the studies that have been performed, patients were not preselected for estrogen receptor–positive (ER^+) or progesterone receptor–positive (PgR^+) tumors, which are the most responsive.[5] Nevertheless, it is now evident that tamoxifen and the third-generation aromatase inhibitors, letrozole, anastrozole, and exemestane, are active in this treatment setting.[6–10] Two interesting examples are illustrated in Figs. 1 and 2. Mammograms of a patient with locally advanced inflammatory breast cancer, obtained before and after 3 months of neoadjuvant treatment with letrozole, demonstrate marked resolution of edema (Fig. 1). Dramatic improvement was also seen after 3 months of neoadjuvant letrozole in a patient with an ulcerated primary breast tumor (Fig. 2). To date, a single randomized phase III trial has compared two neoadjuvant endocrine therapeutic agents, letrozole and tamoxifen, and letrozole was shown in this study to be more effective.[11,12]

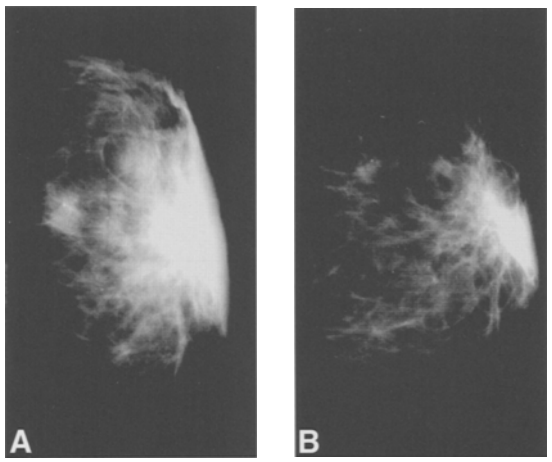

FIG. 1. Mammograms of the breast of a patient with locally advanced inflammatory breast cancer, before (**A**) and after (**B**) neoadjuvant treatment with letrozole for 3 months.

The results of that trial (024) are discussed in detail by Ellis in this supplement.

Our group at the Edinburgh Breast Unit has conducted another, albeit small, randomized trial of neoadjuvant endocrine therapy in postmenopausal women with large primary breast cancers, for which results are now available for a 10-year follow-up period. One hundred seventy-one patients were accrued between January 1990 and October 1995. The trial design is shown in Fig. 3. Initially, patients were accrued who had primary tumors >4 cm in size, a requirement which was later changed to >3 cm. Patients were randomized to either the standard treatment arm (n = 86) or the experimental arm (n = 85). Standard treatment was surgery with or without radiation therapy (RT), followed by chemotherapy for premenopausal women who were lymph node–positive (LN^+), or tamoxifen for premenopausal women who were node-negative (LN^-) and all postmenopausal patients (both LN^+ and LN^-).

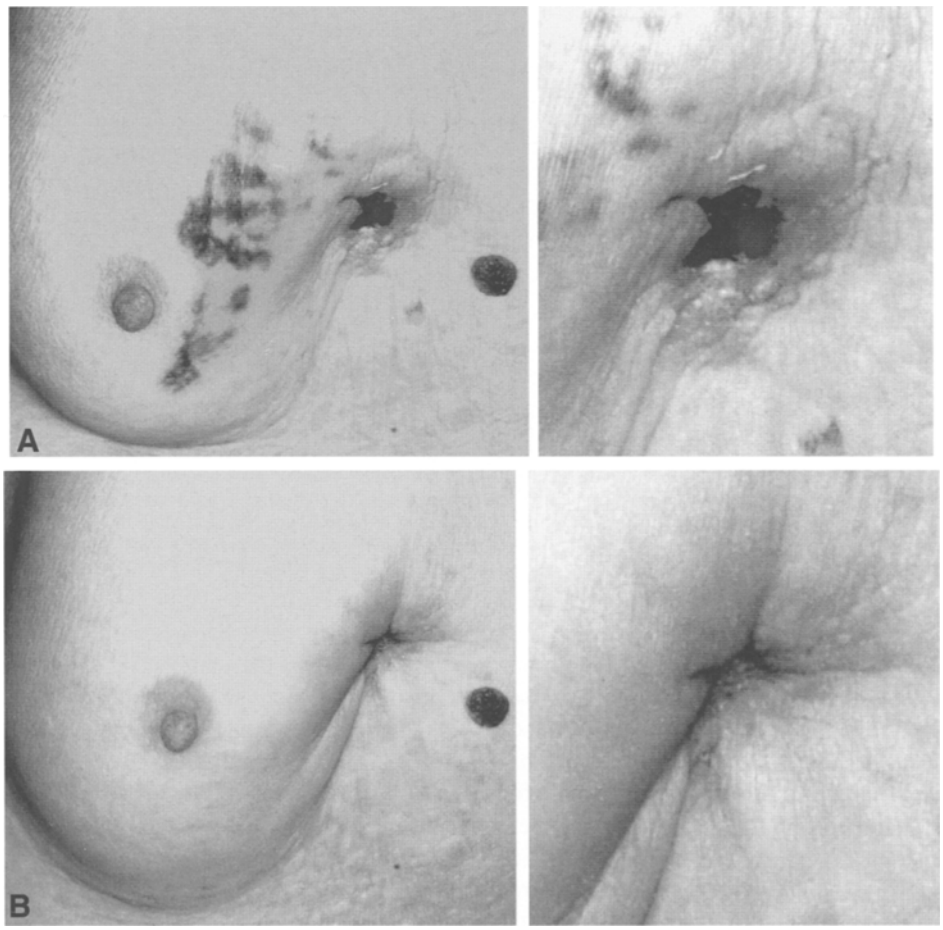

FIG. 2. A patient with an ulcerated primary breast cancer at presentation (**A**, low-power and higher-power views), and after 3 months of neoadjuvant letrozole treatment (**B**). The tumor was initially 35 × 32 × 22 mm in size by ultrasound imaging; after treatment, the tumor was reduced to 14.6 × 14.4 × 13.3 mm, and the patient underwent successful breast-conserving surgery.

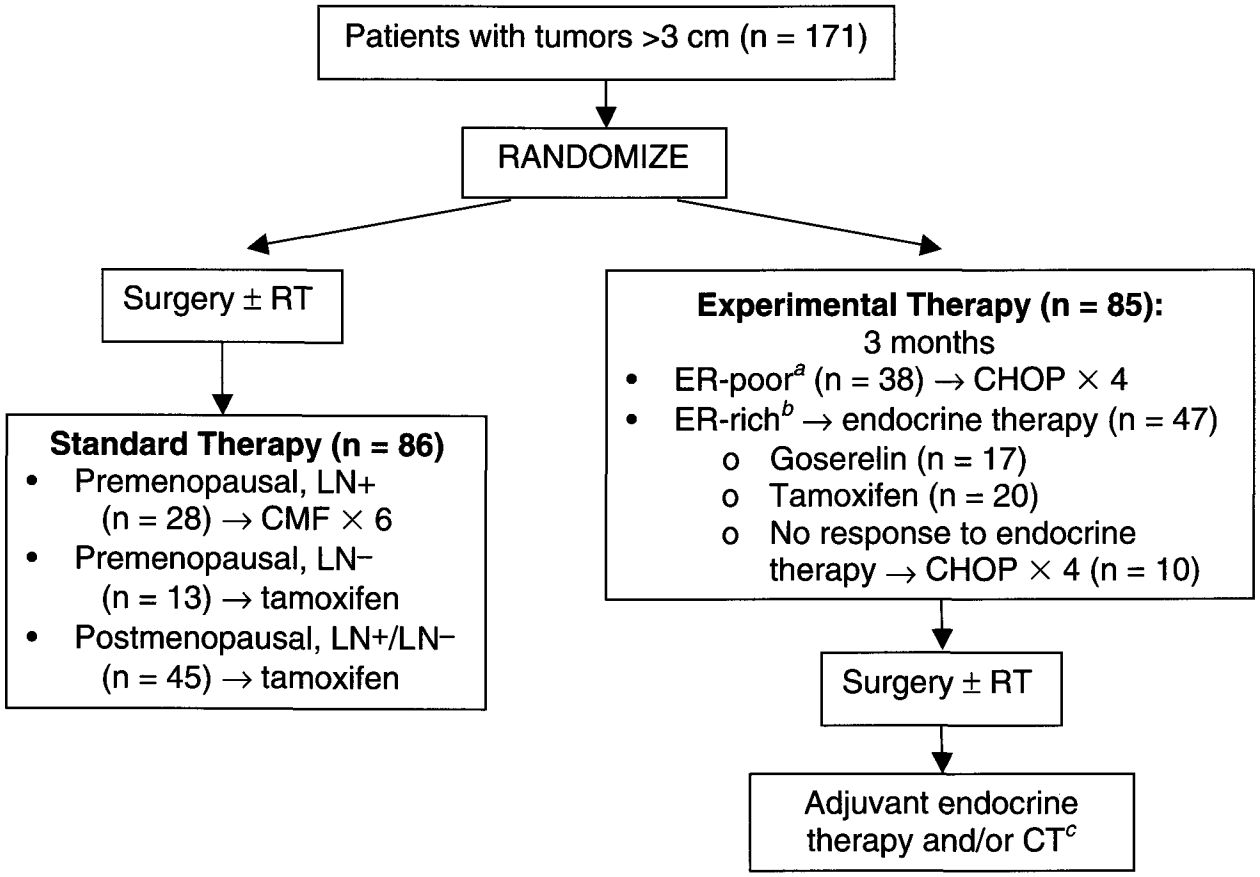

FIG. 3. Design of our randomized trial of neoadjuvant therapy (experimental therapy) versus conventional surgery, with or without radiation therapy, followed by adjuvant systemic therapy (standard therapy) for large primary breast cancer. Standard and experimental therapy was given to patients who were lymph node–positive or –negative, with standard therapy differing according to nodal status (RT, radiation therapy; LN, axillary lymph nodes; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; ER, estrogen receptor, CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CT, chemotherapy).

Experimental treatment consisted of 3 months of neoadjuvant endocrine treatment for patients with tumors that had high ER expression (ER-rich; ≥20 fmol/mg cytosolic protein) or chemotherapy for patients with tumors that were ER-poor or ER-negative (<20 fmol/mg); patients for whom endocrine therapy failed then received chemotherapy. Experimental preoperative endocrine therapy consisted of goserelin or tamoxifen; in the absence of response, patients switched to chemotherapy. Experimental treatments were followed by surgery, with or without RT, and then postoperative endocrine therapy and/or chemotherapy. Responders to endocrine therapy continued receiving the same therapy postoperatively; those who did not respond to initial endocrine therapy and were switched to chemotherapy received a further two cycles of the same chemotherapy postoperatively.

Despite the small scale of this study, the survival results at 10 years of follow-up revealed that primary systemic therapy, including endocrine therapy for patients with ER-rich tumors, afforded the same or greater advantage than conventional postoperative treatment only. For the experimental versus conventional treatment arms overall, metastasis-free survival favored the experimental arm, although statistical significance was not reached ($P = .07$).

The patient group was small, but overall survival was at least equivalent in the two arms, as was survival in the ER-rich subpopulation, and some additional conclusions could be drawn: Axillary lymph node status following primary systemic therapy was the best indicator of treatment outcome, and treatment with chemotherapy after failed endocrine therapy was not obviously beneficial. One of the factors we found to be predictive of poor response to neoadjuvant chemotherapy was an ER+ status but failure to respond to prior endocrine therapy. This finding, along with those of other studies,[12] underscores the need to find early markers of endocrine resistance, so that chemotherapy can be used up front for patients with tumors that are inherently resistant.

PATIENT SELECTION FOR NEOADJUVANT ENDOCRINE THERAPY

Some of the recognized criteria that should influence any consideration of neoadjuvant endocrine therapy for large primary breast cancers are indicated in Table 1. Women who are postmenopausal and have inoperable and ER-rich tumors are obvious choices. Patients who would be eligible for breast-conserving surgery if tumor shrinkage occurs should also be candidates, but patients who need a mastectomy are unsuitable because some patients have multiple tumor foci or a large tumor adjoining extensive area of ductal carcinoma in situ.

The Edinburgh neoadjuvant hormonal therapy protocol consists of 3 months of treatment following a biopsy at diagnosis, with monthly clinical and ultrasound examinations; patients who are postmenopausal and have ER-rich tumors are eligible. We have obtained dramatic shrinkage in cases of large, locally advanced breast cancers, including cases of inflammatory disease (Fig. 1) and ulceration (Fig. 2), using single-agent letrozole during this period, which has then enabled breast-conserving surgery with excellent cosmetic results. Other third-generation aromatase inhibitors have also been highly effective.[10]

The 024 study of neoadjuvant letrozole versus tamoxifen demonstrated significantly higher rates of response and breast-conserving surgery among patients treated with letrozole than among patients who received tamoxifen.[11,12] As in that study, we have found that response to letrozole, assessed as median tumor volume reduction either by clinical palpation or by ultrasound imaging, is significantly greater in tumors with the highest level of ER expression (Allred score of 8 versus 6/7 combined). Such patients achieved a median volume reduction of about 80% by clinical examination (Fig. 4).[4,13]

In our experience at Edinburgh with the experimental treatment, wide excisions were performed, with a very low rate of failure: 2/107, or 1.8%. By comparison, much higher failure rates (16%–62%) have been reported after neoadjuvant chemotherapy, due to multiple tumor foci or involved margins.[5,14,15] With regard to incidence of local recurrence following neoadjuvant endocrine therapy and surgery, we have found that both aromatase inhibitor and tamoxifen treatment yield high 5-year recurrence-free survival and overall survival rates if breast-conserving surgery is followed by RT.

TABLE 1. *Patient selection criteria for neoadjuvant endocrine therapy for breast cancer in the Edinburgh Breast Unit*[4]

Postmenopausal
ER-rich: Histoscore ≥80 (range, 140–300), Allred score 6–8; or ≥20 fmol/mg cytosolic protein
Locally advanced inoperable disease
Large operable tumor requiring downstaging for breast-conserving surgery

FACTORS PREDICTING RESPONSE OR RESISTANCE TO ENDOCRINE NEOADJUVANT THERAPY

In an effort to identify predictors of response versus resistance to endocrine therapy with tamoxifen or letrozole, tumor biopsy specimens taken before and 10 to 14 days and 3 months after the start of preoperative treatment are being evaluated for degree of cell proliferation, based on expression of the Ki67 proliferation marker. Responders

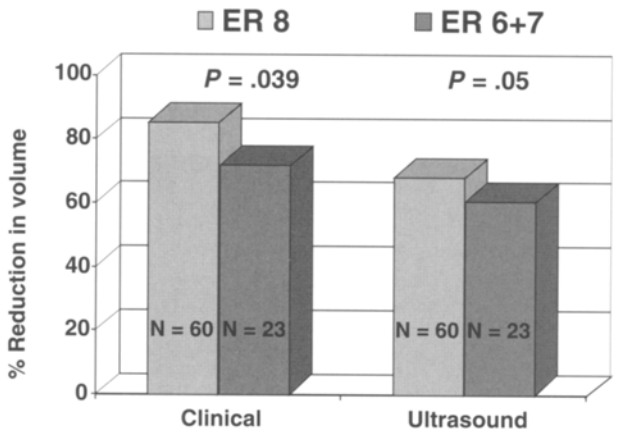

FIG. 4. Median tumor volume changes following 3 months of neoadjuvant therapy with letrozole, measured either by clinical palpation or by ultrasound imaging, for subcategories of primary breast cancers that had the highest level of ER expression (Allred score of 8 [ER 8]; n = 60) versus lower expression levels (scores of 6 and 7 combined [ER 6+7]; n = 23). Percent volume reductions were significantly greater for ER 8 tumors, for either method of tumor size determination.[13]

to tamoxifen show significant reductions in the median percentages of proliferating cells, after 10 to 14 days and after 3 months. In contrast, in nonresponders there was a slight increase in proliferating cells at both time points (Table 2). Similarly, after 14 days of letrozole treatment, there was a decrease in the percentage of Ki67-positive cells in all 13 ER+ tumors examined (Fig. 5).[16]

These results have prompted us to compare the effectiveness of different endocrine agents by evaluating short-term effects on cell proliferation and on other biological markers in 10- to 14-day biopsies. A 14-day study (FemarA) comparing letrozole and anastrozole effects in 200 postmenopausal women with operable ER+ tumors has been completed in the Edinburgh Breast Unit, based on fixed and fresh tumor biopsies. These results should be available by mid-2004.

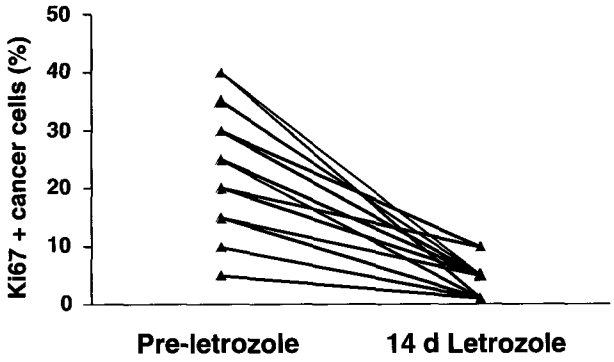

FIG. 5. Changes in percentage of primary breast cancer cells positive for the Ki67 proliferation marker after 14 days of neoadjuvant therapy with letrozole, based on comparison of visible staining in paired pretreatment and 14-day treatment tumor biopsy samples.[16]

SUMMARY

Neoadjuvant endocrine therapy with tamoxifen or an aromatase inhibitor is effective and safe in postmenopausal women with ER-rich locally advanced breast cancer that is either inoperable or operable by mastectomy but appropriate for breast-conserving surgery if tumor shrinkage is obtained. In select patients, response rates are high, and the greatest reduction in tumor volume (more than 80%) occurs in tumors with the highest level of ER expression (Allred score of 8). Neoadjuvant therapy allows more breast-conserving surgery, and local recurrence rates are acceptably low when surgery is followed by RT. Letrozole has been the agent of choice in the Edinburgh Breast Unit in postmenopausal women because of our extensive experience with that agent and its superior efficacy in advanced breast cancer, but other endocrine agents are effective also.

Efforts are under way to identify biomarkers of response versus resistance to neoadjuvant endocrine therapy. So far, reduction in proliferating cells after 14 days of treatment with tamoxifen has shown a good correlation with response and may permit early identification of resistant tumors, so that those patients may be switched to an effective treatment alternative.

TABLE 2. *Changes in proliferating cells relative to response in primary breast tumors during and after neoadjuvant treatment with tamoxifen*

	Percentage proliferating cells (interquartile range) in tumor sample biopsied at		
Patient category	Diagnosis	10–14 d of treatment	3 mo of treatment
Responders (n = 38)	8 (4–18)	3 (2–12) [a]	4 (2–11) [b]
Nonresponders (n = 12)	9 (6–12)	10.5 (7–15)	14 (8–20)

[a] $P = .0015$ in comparison with results in diagnostic biopsy.
[b] $P = .0003$ in comparison with results at diagnosis.

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