Neoadjuvant Endocrine Therapy for Breast Cancer: An Overlooked Option?

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For many oncologists, neoadjuvant treatment for breast cancer is synonymous with preoperative cytotoxic chemotherapy, regardless of tumor characteristics. Preoperative therapy with an endocrine agent is generally considered suitable only for the frail elderly or the medically unfit. However, favorable information regarding third-generation aromatase inhibitors in the treatment of all stages of breast cancer prompts a reconsideration of this bias. In light of the fact that neoadjuvant therapy with aromatase inhibitors is restricted to postmenopausal women with strongly estrogen-receptor–positive tumors, the assumption that neoadjuvant combination chemotherapy is more efficacious than a third-generation aromatase inhibitor can be reasonably questioned. It is particularly remarkable that the outcome of a comparison of adjuvant tamoxifen vs anastrozole (Arimidex)—the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial—in more than 6,000 patients was predicted by a neoadjuvant trial that showed an efficacy advantage for a third-generation aromatase inhibitor (letrozole [Femara]) compared to tamoxifen in a sample of 337 patients after only 4 months of treatment. The potential of the neoadjuvant setting in efforts to identify new biologic agents that could build on the effectiveness of adjuvant aromatase inhibitors is therefore beginning to be appreciated. Finally, neoadjuvant therapy with an aromatase inhibitor could be considered a sensitivity test of endocrine therapy that might be incorporated into strategies to individualize treatment according to response. For this possibility to be realized, however, a better understanding of the relationship between surrogates from the neoadjuvant setting and the long-term outcome of adjuvant aromatase inhibitor therapy will have to be established through practice-setting clinical trials.

Neoadjuvant chemotherapy for breast cancer is indicated for tumors that are not suitable for modified radical mastectomy or to increase the chance of breast-conserving surgery for tumors considered operable only with modified radical mastectomy. However, neoadjuvant therapy has several further advantages besides the potential to improve surgical outcomes in patients with large tumors. First, the response of the primary tumor provides an in vivo test of drug sensitivity, which might be of value in identifying patients at high risk of relapse despite a course of standard adjuvant chemotherapy. Second, repeat sampling of the tumor before and after treatment enables research on the mechanisms of drug action and predictive biomarkers. Unfortunately, however, the theoretical advantage of improved long-term systemic control as a result of neoadjuvant chemotherapy has never been demonstrated in large randomized studies. Thus, neoadjuvant chemotherapy remains a largely optional aspect of breast cancer therapy, except in patients who truly have locally advanced disease. The use of neoadjuvant endocrine therapy is fairly uncontroversial among patients too unfit to receive chemotherapy or who choose not to undergo this more toxic form of treatment. However, for patients who could be reasonably treated with either approach, the knowledge base for the neoadjuvant use of aromatase inhibitors is still too limited for many physicians to accept the routine application of this treatment. For example, an international expert panel convened recently to consider neoadjuvant treatment concluded that hormonal manipulation is not currently a standard of care for preoperative treatment of operable breast cancer but is a "second choice" for selected patients including the elderly, women with impaired organ function, poor performance status, or those who are considered a poor surgical risk, as well as women who are unwilling to accept the side effects associated with chemotherapy. Nonetheless, the panel encouraged research and recommended trials to optimize the neoadjuvant treatment of estrogenreceptor (ER)-positive, locally advanced disease.
Historical Experience With Tamoxifen

Early studies of the use of endocrine therapy for the treatment of primary carcinomas of the intact breast were mostly small, phase II trials of tamoxifen alone without surgery in elderly or unfit, poor surgical candidates.[5] The majority of patients in these studies did not undergo definitive surgery, and hormone-receptor expression analysis was not an eligibility criterion. These issues probably account for the poor long-term results and contributed to the misconception that endocrine treatment of primary breast cancer is not efficacious. For example, in one study, more than 60% of patients treated with primary tamoxifen therapy developed progressive disease after 5 years, although almost 50% initially responded to treatment.[6] It was, therefore, no surprise that a meta-analysis of the long-term results of two trials comparing primary tamoxifen to initial surgery followed by tamoxifen demonstrated that primary tamoxifen therapy was associated with an increased risk of death from breast cancer.[7] Clearly, primary tamoxifen therapy is a suboptimal therapeutic approach that can almost never be recommended. It is fair to argue that a similar result would have been achieved with chemotherapy alone because, in follow-up, patients with good initial responses to neoadjuvant chemotherapy also show poor local control without definitive surgery.[8] Unquestionably, surgery remains an indispensable aspect of the management of breast cancer regardless of the nature of the neoadjuvant therapy. Although interest in primary tamoxifen therapy waned as a result of these data, interest persisted in the use of tamoxifen for a few months as neoadjuvant therapy in older patients with ER-positive disease. For example, a study in Edinburgh treated 100 patients over the age of 70 with ER-rich breast cancers.[9] Using volume reductions determined by ultrasound as a measure of response, 73 patients experienced significant tumor regression. Similar conclusions regarding an acceptable level of efficacy for neoadjuvant tamoxifen therapy in older patients were drawn from a smaller study conducted at the M. D. Anderson Cancer Center.[10]

Neoadjuvant Aromatase Inhibitor Therapy

The introduction of third-generation aromatase inhibitors encouraged further research on neoadjuvant endocrine treatment. An initial phase II experience with neoadjuvant letrozole (Femara) in Edinburgh was encouraging, with a response rate of 92% documented in 24 postmenopausal women with ER-positive, locally advanced breast cancer treated for 3 months prior to surgery.[11] All 15 patients who initially required mastectomy were subsequently able to undergo breast conservation. The same investigators recently reviewed their phase II experiences in more than 100 patients treated with 3 months of tamoxifen, letrozole, anastrozole (Arimidex), or exemestane (Aromasin).[12] Their conclusion that aromatase inhibitors were likely to be more effective neoadjuvant therapy than tamoxifen stimulated the activation of several randomized controlled trials to confirm this hypothesis. Letrozole

The first and currently only adequately powered study to report to date was a randomized, double-blind, multicenter study (Letrozole 024) that compared the activity of 4 months of preoperative letrozole vs tamoxifen in 337 postmenopausal women with ER- and/or progesterone receptor (PR)-positive breast cancer.[13] At baseline, none of the patients were eligible for
breast-conserving surgery, with 14% considered inoperable. The letrozole group had a significantly higher objective clinical response rate compared to the tamoxifen group (55% vs 36%, \( P < .001 \)). Secondary end points that supported this conclusion included ultrasound response (35% vs 25%, \( P = .042 \)), mammographic response (34% vs 16%, \( P < .001 \)), and breast-conserving surgery rates (45% vs 35%, \( P = .022 \)). In a prospective central analysis of hormone-receptor status, a small number of ER- and PR-negative tumors were detected. This led investigators to modestly underestimate the value of neoadjuvant endocrine treatment, and the adjusted analysis is presented in Table 1. This study also illustrated the strong relationship between ERexpression levels (determined by the Allred score) and the likelihood of response (Figure 1). As long as ER is expressed at high levels (Allred score of 7 and 8), response rates of 60% to 70% can be expected. **Anastrozole**

Preliminary data on neoadjuvant anastrozole have also been reported. Only one of these studies has been published in the peer-reviewed literature,[14] and most of the ongoing investigations carry caveats associated with abstract presentations and single-institution experiences. A recently reported Russian study randomized 87 postmenopausal women with ER-rich tumors to anastrozole, tamoxifen, or the combination of anastrozole and tamoxifen for 3 months.[15] Anastrozole was superior to both tamoxifen and the combination in overall response rates by clinical palpation, mammography, and ultrasound (70% vs 44% vs 49%, \( P = .048 \); 55% vs 36% vs 40%, \( P = .058 \); 44% vs 30% vs 32%, \( P = .072 \), respectively) with a trend toward higher breast-conservation rates (42% vs 28% vs 30%, \( P = .056 \)). The ongoing Immediate Preoperative Arimidex Compared to Tamoxifen (IMPACT) trial is evaluating anastrozole, tamoxifen, and the combination in 330 postmenopausal women with ER-positive operable breast cancer.[16-18] Updated results of this study were reported at the San Antonio Breast Cancer Symposium in December 2003. In terms of response rates, anastrozole and tamoxifen were no different, although suppression of Ki67 and rates of breast-conserving surgery were greater with anastrozole. One important feature of the IMPACT trial is that inoperable breast tumors are excluded (unlike the Letrozole 024 study). As a result, crosstrial comparisons of response rates may be misleading.

![Graph showing response rates for letrozole and tamoxifen](image)

**Figure 1:** The Letrozole 024 Study—Clinical response rates for letrozole and tamoxifen from the Letrozole 024 study, showing a clear correlation between tumor response and estrogen-receptor (ER) Allred score. Adapted, with permission, from Ellis MJ et al: *J Clin Oncol* 19:3808-3816, 2001, and with permission from the American Society of Clinical Oncology.

**Exemestane**

The efficacy of exemestane was evaluated in 13 postmenopausal women with untreated large or
locally advanced ER-rich tumors after a 3-month treatment period. Treatment was associated with a marked reduction in aromatization in nonmalignant breast tissue in every patient and in breast tumor tissue in all but one patient. The median reduction in tumor volume by clinical examination, ultrasound, and mammography was 85.5%, 82.5%, and 84%, respectively. Of 10 patients who initially required mastectomy, 8 were able to undergo breast-conserving surgery after treatment.[19] A Spanish multicenter study recently evaluated the efficacy of 6 months of exemestane in 33 women over 65 years old with ER-rich tumors larger than 3 cm and reported a response rate of 50% in the first 28 patients.[20] These preliminary data support further studies of exemestane as neoadjuvant therapy. **Summary of Findings**

In conclusion, the promising randomized data on letrozole will soon be supplemented by peer-reviewed information on anastrozole and exemestane. An outstanding question concerns the optimal duration of preoperative endocrine therapy. Interestingly, preliminary data on patients given a maximum of 8 months of preoperative letrozole showed a response rate of 90% vs 57% for those receiving 4 months of treatment.[21] Larger randomized studies will be necessary to determine the optimal duration of aromatase inhibitor therapy for tumors that have responded by 4 months, but the tamoxifen experience would suggest that for nonresponding tumors further delays in surgery are inappropriate. **Indirect Comparison of Neoadjuvant Endocrine Therapy and Chemotherapy**

Postmenopausal women with hormone-receptor-positive breast cancer derive most adjuvant benefit from endocrine treatment rather than chemotherapy.[22,23] On this basis, neoadjuvant endocrine therapy is a logical approach to investigate in this patient subpopulation. The design of a practice-setting trial that would compare neoadjuvant therapy with an aromatase inhibitor (investigational arm) to chemotherapy (standard therapy arm) requires an estimate of the efficacy of neoadjuvant chemotherapy. Data on this issue are difficult to compile, however, because the results of trials of neoadjuvant chemotherapy are not often reported according to age, hormone-receptor status, and age. In addition, neoadjuvant chemotherapy studies, like breast cancer studies in general, enroll very few women over age 70. Arguably, robust data on the effectiveness of neoadjuvant chemotherapy in postmenopausal women with strongly ER-positive disease simply do not exist.
Figure 2: Relationship Between Response and Survival—Survival curves for breast cancer patients, according to response to primary tamoxifen therapy. Adapted, with permission, from Horobin et al.[6]
One of the most striking advantages of neoadjuvant therapy with aromatase inhibitors over chemotherapy is the lower toxicity level. Aside from short-term reversible side effects, chemotherapy-associated leukemia and cardiomyopathy are more common in older patients and should be taken into account when considering the risk-benefit ratio for the administration of cytotoxic drugs in postmenopausal women. A hypothetical advantage of neoadjuvant endocrine therapy is that it can be regarded as an in vivo sensitivity test of endocrine therapy. Patients who achieve a response might have a better chance of survival and could perhaps avoid chemotherapy. Although preliminary data support the hypothesis that patients with primary tumors that respond to tamoxifen survive longer than nonresponders (Figure 2),[6] large-scale studies will be required to generate more confident predictions regarding the relationship between response to neoadjuvant aromatase inhibitor therapy and survival from breast cancer. 

Neoadjuvant Anthracycline-Based Chemotherapy in ER-Positive Disease

In unselected patients, anthracycline-based neoadjuvant chemotherapy is associated with a high response rate. However, evidence shows that responsiveness is attenuated (to < 5%) in ER-positive disease. For example, in an M. D. Anderson Cancer Center study of neoadjuvant chemotherapy with FAC (fluorouracil [5-FU], doxorubicin [Adriamycin], and cyclophosphamide [Cytoxan, Neosar]), of 43 patients who achieved a complete pathologic response after four cycles, only 3 had ER-positive disease. Since the total number of known ER-positive tumors in this data set was 106, the pathologic complete response rate can be calculated to be only 2.8% with this regimen.[24]

Improvements in Surgical Outcomes

Even though the pathologic complete response rate is low, the degree of tumor regression with neoadjuvant aromatase inhibitor therapy is unquestionably sufficient to improve surgical outcomes. In the Letrozole 024 study, all patients were either ineligible for breast-conserving surgery or were deemed inoperable at baseline. T2 tumors were included only if they were considered ineligible for an initial attempt at breast-conserving surgery. After treatment with letrozole, 45% of patients underwent successful breast-conserving surgery, with the rate increasing to 61% among patients with T2 tumors. Comparable estimates with neoadjuvant chemotherapy are difficult to make because the rate of conversion to breast-conserving surgery is not usually reported according to ER status, age, or menopausal status. In addition, many neoadjuvant chemotherapy trials, including the
National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial, included a large number of small tumors eligible for lumpectomy at baseline. Table 2 compares the intended and actual surgical outcomes in NSABP B-18 and Letrozole 024. This comparison must exclude T1 tumors, which were not studied in the Letrozole 024 trial, and arguably T2 tumors as well, because NSABP B-18 allowed the entry of T2 tumors that were eligible for breast conservation at presentation. Only 3% of patients with > T2 tumors were considered eligible for breast-conserving surgery in NSABP B-18, but 22% of these individuals underwent breast conservation after four cycles of neoadjuvant AC (doxorubicin, cyclophosphamide) chemotherapy.[31] In the comparable group of > T2 tumors in the Letrozole 024 study, 29% were eligible for breast conservation. One can therefore argue that four cycles of AC in unselected patients and 4 months of letrozole in postmenopausal women with ER-positive disease are broadly similar in efficacy, in terms of improvements in surgical outcomes.

### Onset of Response

It is often stated that combination chemotherapy has a more rapid onset of action than endocrine therapy and that this is an advantage for chemotherapy. The median time to response was 66 days for letrozole and 70 days for tamoxifen in the Letrozole 024 study; ie, half of the tumors designated as in partial or complete remission at 4 months had already met response criteria at 2 months.[13] This suggests that for some tumors at least, the response to aromatase inhibitor therapy is fairly rapid. Time to response is rarely quoted in the neoadjuvant chemotherapy literature, and thus, indirect comparisons are once again difficult to make. **Long-Term Success of Neoadjuvant Treatment-Assisted Breast Conservation**

Data on the long-term outcome of patients given neoadjuvant aromatase inhibitors are sparse at present, and this is certainly the major obstacle to widespread adoption of this treatment approach. Reassuring data regarding local recurrence rates are emerging from patients treated in Edinburgh, where breast-conserving surgery after neoadjuvant endocrine therapy produced excellent local control rates as long as the breast was treated with radiotherapy (Table 3).[12] **Biomarker Research** The molecular basis for the response of hormone-receptor-positive disease to endocrine treatments is poorly understood. Neoadjuvant endocrine therapy trials, therefore, provide a critical opportunity to conduct correlative science studies that address this question. **Protein Biomarkers**

The initial phase of these investigations has focused on protein biomarker levels estimated by immunohistochemistry, including the proliferation marker Ki67, tyrosine kinase-linked peptide growth-factor receptors, epidermal growth-factor receptors HER1 and HER2, and the estrogen-regulated proteins, trefoil factor 1 (TFF1), ER, and PR. Analysis of these biomarkers can be viewed from two perspectives: first as baseline predictors of response, and second as pharmacodynamic biomarkers of the effect of neoadjuvant endocrine therapy. One of the more interesting results concerning baseline predictors of response was the finding that differences in neoadjuvant response rates between letrozole and tamoxifen were particularly marked for tumors that were ER-positive and also positive for HER1 and/or HER2 by immunohistochemistry (88% vs 21%, respectively; \(P = .0004\)).[32] This suggests that tumors in this category are very sensitive to estrogen-deprivation therapy but somewhat resistant to tamoxifen. Theoretically, therefore, HER1 and HER2 analysis could be used to identify subgroups of patients in whom an aromatase inhibitor should be favored over tamoxifen as adjuvant therapy. An investigation is currently under way with tissue blocks obtained from patients who received treatment in the context of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial to further investigate this hypothesis (personal communication, Prof. M. Dowett, 2003). Given that the pathologic complete response rate is low with
Neoadjuvant aromatase inhibitor therapy, alternative clinical or biomarker surrogates for therapeutic efficacy must be identified. Levels of Ki67, a cell-cycle-regulated protein, typically fall with neoadjuvant endocrine treatment, and this compound was recently shown to be suppressed more effectively by letrozole than by tamoxifen in samples from the Letrozole 024 trial.[33] This finding correlates well with the clinical advantages of third-generation aromatase inhibitors in the neoadjuvant, adjuvant, and advanced disease settings[34] and supports a role for Ki67 as a surrogate end point in phase III neoadjuvant studies that aim to improve upon the efficacy of single-agent aromatase inhibitor treatment. Levels of the estrogen-regulated proteins PR and TFF1 also fall dramatically with letrozole in contrast to tamoxifen therapy, which, if anything, produces a trend for an increase in PR.[33] These observations underscore the profound differences in tumor gene regulation that take place when tumors are treated with estrogen deprivation as opposed to a selective estrogen-receptor modulator (SERM). Another finding from these investigations was that tamoxifen treatment caused profound downregulation of ERs in some tumors; in posttreatment samples, ER levels were lower in the tamoxifen arm than in the letrozole arm. These data suggest that the mechanism responsible for ER downregulation with SERM therapy is different from that of aromatase inhibitors, and ER levels should be interpreted with caution in posttreatment samples.[33]

**Gene Expression**
Currently, gene expression profiling is under investigation both as a means of discovering new biomarkers for responsiveness to aromatase inhibitor therapy, and to better understand the molecular basis of response to these agents.[35] Limited microarray information from a responding case in an ongoing phase II investigation of letrozole can be presented to illustrate how estrogen deprivation downregulates expression from multiple genes involved in critical pathways that drive the neoplastic phenotype (Table 4).
Genes showing the greatest decrease with treatment included members of a proliferation cluster (topoisomerase II alpha (170 kD), ribonucleotide reductase M2 polypeptide, 5-methyltetrahydrofolate-homocysteine methyltransferase reductase, and cell division cycle 2, G1 to S and G2 to M, an invasion cluster (matrix metalloproteinase 1 [interstitial collagenase]), carboxypeptidase B1 (tissue), CD36 antigen (collagen type I receptor, thrombospondin receptor), protein regulator of cytokinesis 1, and a cell survival cluster (baculoviral IAP repeat-containing 5 [survivin]), and nucleolar protein 3 (apoptosis repressor with CARD domain) This ongoing study is powered to explore baseline gene expression profiles to delineate "metagenes" that identify patients with the greatest chance of responding to neoadjuvant aromatase inhibitor therapy.[36] The long-term goal will be to determine if these same metagenes predict the risk of relapse in patients.
Future

Prospects: Currently, no ongoing studies are investigating neoadjuvant endocrine therapy with the same rigor applied to neoadjuvant chemotherapy. Ultimately, a practice-setting trial along the lines of NSABP B-18 will be necessary. A potential study design is outlined in Figure 3. Eligible patients would be stratified according to whether chemotherapy is considered necessary. Typically, these patients would be those with T2 or larger tumors, those with positive sentinel nodes, and those who require neoadjuvant neoadjuvant therapy anyway. For these patients, the randomization would be between neoadjuvant chemotherapy and an aromatase inhibitor. For patients randomized to receive neoadjuvant aromatase inhibitors, chemotherapy would be administered postoperatively so that exposure to chemotherapy was balanced between the two arms. For patients who do not require chemotherapy—typically those with sentinel node-negative T1 and small T2 tumors, or those in whom chemotherapy would be inappropriate—randomization would be between immediate surgery and neoadjuvant aromatase inhibitor therapy. Like NSABP B-18, the study could be powered to observe a survival advantage for neoadjuvant endocrine therapy. The hypothesis that neoadjuvant endocrine therapy improves survival in this setting was first proposed by B.J. Kennedy in a 1957 paper in which...
he and his colleagues described the remarkable efficacy of high-dose estrogen therapy for locally advanced breast cancer in older patients.[37] Later studies have suggested that high levels of circulating estrogen at the time of surgery may adversely affect long-term outcomes in premenopausal women with breast cancer and ablating ovarian function at the time of mastectomy could be therapeutic.[38-40] In postmenopausal women, the hypothesis that the endocrine milieu at the time of surgery affects long-term outcome could be easily addressed by randomizing patients to receive preoperative aromatase inhibitors or not. Given the remarkable effects of estrogen deprivation on ER-positive disease (illustrated by the dramatic changes in global gene expression and proliferation cited in this paper), this hypothesis seems increasingly tenable. Current trials are focusing on ways to further improve responses to neoadjuvant aromatase inhibitor therapy. This could be achieved either by using new predictive biomarkers to exclude patients with a poor chance of responding (as described above), or through the addition of a second agent that could enhance the antineoplastic effect of estrogen deprivation. Biologic therapies currently slated for testing in combination with aromatase inhibitors include cyclooxygenase-2 (COX-2) inhibitors as adjuvant therapy and HER1 and HER2 tyrosine kinase inhibitors, farnesyl transferase inhibitors, and mammalian target of rapamycin (mTOR) inhibitors in the advanced disease setting. NCI-C MA.27

At the time of this writing, a new randomized neoadjuvant endocrine therapy trial is being activated. The National Cancer Institute of Canada (NCI-C) has launched a US Breast Intergroup adjuvant trial to compare the nonsteroidal aromatase inhibitor anastrozole with the steroidal inhibitor exemestane. In a two-by-two randomization, patients will also receive the COX-2 inhibitor celecoxib (Celebrex) or placebo. Celecoxib appears to be potentially additive with exemestane in both treatment and prevention preclinical models.[41-43] Potential antitumor mechanisms include inhibition of prostaglandin E2, induction of aromatase, antiangiogenesis effects, inhibition of tumor invasion, and inhibition of tumor-induced inflammation and growth-factor production. ACOSOG Z1031 Tri

In a parallel clinical trial, the American College of Surgeons Oncology Group (ACOSOG) is considering the activation of a randomized placebo-controlled neoadjuvant trial in which postmenopausal patients with ER-positive surgical stage II/III breast cancer will receive 4 months of exemestane and placebo or exemestane in combination with celecoxib at 400 mg bid (the proposed schema is shown in Figure 4). This trial would provide an important new opportunity to determine whether small studies in the neoadjuvant setting consistently predict the outcome of large adjuvant trials.

**Conclusions** The results of the ATAC trial are beginning to show an advantage for adjuvant aromatase inhibitor therapy over tamoxifen, but currently this improvement is rather modest, with an absolute reduction in relapse-free survival of only 2% to 3%.[44] If we are to make more dramatic improvements in treatment, we must deal with the problem of endocrine therapy resistance. The broader significance of neoadjuvant endocrine therapy, therefore, lies in the marriage of the new scientific possibilities of genomics and proteomics and a clinical context in which tumor profiling can be explored according to the response of ER-positive breast cancer to the simplest, oldest, and most successful breast cancer therapy of all-estrogen deprivation.

**Disclosures:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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