Neoadjuvant Endocrine Therapy for Breast Cancer: Medical Perspectives

Matthew J. Ellis
Duke University Breast Cancer Program, Duke University Medical Center, Durham, North Carolina 27710

Abstract
The indolent nature of estrogen-dependent breast cancer is the most important obstacle for development of new adjuvant endocrine treatments. Clinical trials require thousands of study participants and at least a decade of clinical investigation. How can we be sure that a new endocrine agent warrants this extraordinary level of investment? Traditionally, we have relied on advanced breast cancer trials to determine which drugs are suitable for adjuvant studies. However, with endocrine agents the high incidence of resistance in metastatic breast cancer may mask important advances in efficacy. Recent clinical results with the aromatase inhibitor letrozole suggest that neoadjuvant endocrine therapy is a highly informative additional approach to consider when planning adjuvant studies. In this report, new neoadjuvant endocrine therapy study designs are discussed that address the following issues: (a) the scientific opportunities afforded by gene microarray studies and other genetic technologies to investigate the molecular basis of estrogen-dependent breast cancer; (b) studies that address critical drug development questions as a prelude to adjuvant studies; and (c) the conduct of randomized trials that compare neoadjuvant chemotherapy with neoadjuvant aromatase inhibitor therapy to establish a place for neoadjuvant endocrine therapy in routine clinical practice.

Neoadjuvant Endocrine Therapy versus Neoadjuvant Chemotherapy
Neoadjuvant endocrine therapy has a long and interesting clinical history. The first description of primary breast cancer treatment with an endocrine agent was in 1957 when Kennedy et al. described successful treatment of locally advanced disease with diethylstilbestrol (1). After the introduction of tamoxifen, numerous trials examined the effect of this antiestrogen on primary breast cancer, but these studies were not true neoadjuvant protocols, i.e., addressing the use of preoperative tamoxifen to improve surgical outcomes. Most randomized investigations focused on the concept of primary tamoxifen therapy for older patients. Here the clinical intent was to replace initial breast surgery and radiation with long-term tamoxifen treatment, with definitive surgery and radiation reserved for patients who suffered local progression. Poor local control in these trials indicated that primary tamoxifen therapy is suitable only for the most frail and infirm patients who are unable to tolerate surgery and are unlikely to live long because of comorbid illness (see Ref. 2 for a review). The more recent studies described in this report have refocused attention on neoadjuvant endocrine treatment and particularly on aromatase inhibitors, because these agents have considerable clinical activity in this clinical setting. As one thinks about these studies, it hardly needs stressing that the biological and pharmacological basis for neoadjuvant endocrine therapy and neoadjuvant chemotherapy are very different. From a clinical perspective, perhaps the most obvious issue is that the entire adjuvant effect of neoadjuvant chemotherapy occurs during neoadjuvant treatment phase. The opposite is true for neoadjuvant endocrine therapy because the preoperative phase provides only a small fraction of the total drug exposure (because all patients receive 5 years of postoperative treatment). One consequence of this fundamental difference is that pathological complete responses are uncommon with neoadjuvant endocrine therapy, but this should not necessarily be viewed as a disadvantage as long as tumors regress sufficiently to allow an improvement in surgical outcomes. Furthermore, alternative biomarkers to pathological complete responses will need to be explored in neoadjuvant endocrine therapy trials to help us to predict the likelihood of long-term disease-free survival with the endocrine agent. Early experience with tamoxifen does suggest a relationship between clinical response in the primary tumor and the likelihood that adjuvant tamoxifen treatment will control systemic disease (3). Other, potentially more reliable, predictive biomarkers could be easily analyzed after neoadjuvant endocrine therapy including proliferation rate, radiological changes, and modulation of gene expression.

Neoadjuvant Endocrine Therapy Trials with Anastrozole and Exemestane. By the mid-1990s the development of selective aromatase inhibitors had reached a stage where direct comparisons with tamoxifen were warranted. At that point several neoadjuvant endocrine therapy investigations were initiated, driven by the opportunity to obtain tumor tissue before and after treatment so that both baseline predictive markers and surrogate markers for the effectiveness of endocrine therapy could be investigated. Currently, information on the activity of neoadjuvant anastrozole and exemestane are limited to Phase II studies. The group at Edinburgh conducted a randomized double-blind study of 24 patients that examined 1 mg and 10 mg of anastrozole per day for 3 months. The average reduction in tumor volume was 89.3% (ultrasound measurements). In this study there were 15 patients who would have been expected to require a mastectomy at the outset of the study, who were subsequently able to undergo breast conservation after 3 months of treatment (4). These data encouraged initiation of a 300-patient randomized study in which tamoxifen is being compared with anastro-
Letrozole, as well as with the combination of the two drugs (5). Neoadjuvant endocrine therapy with exemestane has also shown promising activity in a very small Phase II study, but to date no randomized comparisons with neoadjuvant tamoxifen have been reported (6).

A Phase III Study Comparing Letrozole and Tamoxifen. A Phase II study of neoadjuvant letrozole in Edinburgh was also encouraging (7), opening the way for a randomized comparison with tamoxifen (8). A total of 337 postmenopausal women with a diagnosis of ER- and/or PgR-positive breast cancer, who were ineligible for breast-conserving surgery, were entered into a protocol that evaluated the efficacy of 4 months preoperative endocrine therapy with either tamoxifen 20 mg/day or letrozole 2.5 mg/day (the Letrozole 024 study). Results showed that 55% of the patients treated with letrozole responded by clinical measurement versus 36% with tamoxifen ($P < 0.001$). Letrozole was also superior to tamoxifen as determined by ultrasound, 35% versus 25% ($P = 0.042$), and by mammography, 34% versus 17% ($P < 0.001$). Logistic regression demonstrated that the odds of achieving a clinical response (CR + PR) were more than twice as high with letrozole than with tamoxifen (odds ratio 2.23; 95% confidence interval of 1.43–3.50; $P = 0.0005$). Finally, more patients underwent breast-conserving surgery when treated with letrozole than with tamoxifen (45% versus 35%; $P = 0.022$; Ref. 9). These results demonstrate that 4 months of letrozole treatment is a viable and nontoxic neoadjuvant regimen that facilitates breast-conserving surgery more effectively than neoadjuvant tamoxifen.

An Adjusted Analysis for Study Biopsy Confirmed ER- and/or PgR-positive Cases. The tumor bank developed during the Letrozole 024 study was used to recheck hormone receptor status. An adjusted analysis performed for a study biopsy to confirm ER- and/or PgR-positive cases suggested that the intent-to-treat analysis modestly underestimated the benefit of preoperative endocrine therapy because of the presence of a small number of ER- and PgR-negative tumors (10). For cases that were confirmed to be hormone receptor-positive the clinical response rate with letrozole was 60%, with 48% of patients undergoing breast-conserving surgery. For both these end points, letrozole remained statistically more efficacious than tamoxifen. Only 8% of patients on the letrozole arm experienced disease progression during preoperative treatment. A summary of these results is provided in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Letrozole</th>
<th>Tamoxifen</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed (ER/PgR)</td>
<td>124 (100%)</td>
<td>126 (100%)</td>
<td></td>
</tr>
<tr>
<td>Overall tumor response (CR + PR)</td>
<td>74 (60%)</td>
<td>52 (41%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>48 (39%)</td>
<td>37 (29%)</td>
<td>0.119</td>
</tr>
<tr>
<td>Mammography</td>
<td>47 (37%)</td>
<td>25 (20%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Breast-conserving surgery</td>
<td>60 (48%)</td>
<td>45 (36%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Clinical disease progression</td>
<td>10 (8%)</td>
<td>15 (12%)</td>
<td>0.303</td>
</tr>
</tbody>
</table>

$^*$ Stratified Mantel-Haenszel $\chi^2$-square test.

Response to Letrozole and Tamoxifen by ErbB1 and ErbB2 Status. Samples from the Letrozole 024 trial were also used to address a long-standing controversy concerning the relationship between ErbB1 (EGFR, epidermal growth factor receptor) and ErbB2 (HER2/new) expression and resistance to endocrine therapies (11–14). The frequency of tumors overexpressing ErbB1 and/or ErbB2, as well as expressing ER ($\geq 10\%$) in the entire analysis (ErbB1+ and/or ErbB2+ and ER+), was 15.2%. Letrozole was considerably more active than tamoxifen in this tumor subset (clinical response rate, 88% versus 21%; $P = 0.0004$), suggesting that overcoming resistance pathways associated with ErbB1 and ErbB2 expression is a significant component of the improvement in outcomes associated with letrozole treatment (Table 2). These results clearly illustrate how neoadjuvant endocrine studies may be used to investigate the impact of biomarker expression on tumor response to set priorities for the development of aromatase inhibitors in the adjuvant setting (10).

Table 2

<table>
<thead>
<tr>
<th>Category</th>
<th>Letrozole</th>
<th>Tamoxifen</th>
<th>Odds ratio (letrozole vs. tamoxifen)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ErbB1+ and ErbB2+</td>
<td>15 of 17</td>
<td>4 of 19</td>
<td>28</td>
<td>0.0004</td>
</tr>
<tr>
<td>ER+</td>
<td>(88%)</td>
<td>(21%)</td>
<td>(4.5–177)</td>
<td></td>
</tr>
<tr>
<td>ErbB1− and ErbB2−</td>
<td>55 of 101</td>
<td>42 of 100</td>
<td>1.7</td>
<td>0.078</td>
</tr>
<tr>
<td>ER+</td>
<td>(54%)</td>
<td>(42%)</td>
<td>(0.9–2.9)</td>
<td></td>
</tr>
</tbody>
</table>

An Adjuvant Trial to Compare Tamoxifen and Letrozole for ER+ and ErbB1+ and/or ErbB2+ Breast Cancer. The difference between neoadjuvant letrozole and tamoxifen observed in patients with ErbB1+ and/or ErbB2+, ER+ breast cancer undergoing neoadjuvant treatment was remarkable but certainly insufficient to set clinical practice in more routine adjuvant and metastatic treatment settings. However, these data point out that establishing the most appropriate endocrine management for ER+ and/or PgR+, ErbB1+, and/or ErbB2+ disease is a priority because adjuvant trials with the ErbB2 inhibitor trastuzumab are under way, with more agents (oral ErbB1 and two tyrosine kinase inhibitors) in the pipeline. The absence of a formal block collection protocol means that retrospective biomarker analyses of the ATAC and BIG/FEMTA adjuvant studies, if they are ultimately possible, will be biased by incomplete block collection, which will underrepresent patients who have died (because consent cannot be obtained) or who entered the trial early on in the accrual process (because the blocks have been discarded). Thus, a prospective study of letrozole versus tamoxifen for ErbB1+ and/or ErbB2+, ER+, and/or PgR+ breast cancer is warranted and has recently been approved by the Cancer and Leukemia Group B (Fig. 1).

ER Cluster Analysis and Prediction of Endocrine Therapy Responsiveness. Estrogen and progesterone receptor analyses are inexact predictive markers for hormone dependence. When both receptors are absent, the chance of a response to endocrine therapy is low. However, hormone receptor-positive tumors are not always responsive to endocrine manipu-
tion. Why is this? The explanation is likely to be complex, and ErbB1 and ErbB2 expression will be only part of the picture. A feasibility study has been completed that successfully demonstrated that ER gene cluster analysis could be undertaken with core needle biopsy samples obtained during neoadjuvant chemotherapy (15). Using Bayesian statistical modeling and neural network theory, it should be possible to sift through several thousands of genes to identify those that more accurately predict response to neoadjuvant therapy than information on ER and PgR status alone.

**Development of New Adjuvant Strategies in the Neoadjuvant Setting.** Small molecule inhibitors of receptor tyrosine kinases are in Phase II development, and some of the first questions that will be asked in the Phase III setting will concern the activity of these agents in combination with endocrine agents. Evidence concerning the activity of letrozole in ER+, ErbB1+, and/or ErbB2+ breast cancer raises optimism over the combination of letrozole with an inhibitor of the ErbB family of receptor tyrosine kinases. Development of these strategies could include a neoadjuvant phase to establish links between clinical outcomes and expression/activity of ErbB1/2, as well as downstream effects of these combinations on gene expression and proliferation. Similarly, the combination of an angiogenesis inhibitor with an aromatase inhibitor as a neoadjuvant regimen is an appealing concept, because inhibition of angiogenesis could reduce metastatic potential before surgery. Another issue that could be addressed in the neoadjuvant setting concerns the comparative activity of aromatase inhibitors and the pure anti-estrogen fulvestrant (Faslodex). Such an investigation might prove useful in determining the likelihood that fulvestrant will be more active than a third-generation aromatase inhibitor as adjuvant treatment.

**A Potential Design for a Randomized Neoadjuvant Trial Comparing Chemotherapy with Letrozole.** A major change in clinical practice in breast cancer requires a trial in which standard therapy is compared with a new approach. In the study outlined in Fig. 2, preoperative chemotherapy would be directly compared with letrozole treatment. Eligibility for the study would be hormone receptor-positive breast cancer with a primary tumor that requires neoadjuvant therapy or if the primary tumor is smaller, cytological (fine needle aspiration) or histological evidence (sentinel nodes) of ipsilateral lymph node involvement. The duration of preoperative chemotherapy would range from 12 to 24 weeks, depending on the regimen chosen. The duration of letrozole treatment would also be flexible, so that partial responders at 4 months would be allowed to continue therapy up to a maximum of 24 weeks before surgery. Patients who experienced a poor response to either approach could either choose immediate surgery or cross over to the opposite arm before surgery. All patients would receive letrozole for 5 years after surgery. For the patients who received preoperative letrozole, consideration would be given to the prognostic information provided by the observed responses. Clearly, patients whose tumors do not respond to letrozole should receive chemotherapy. This would also be administered if, after surgery, a substantial amount of tumor was found in the breast or lymph nodes. However, if, after surgery, the patient’s tumor had undergone a clinical or radiological CR or PR, the nodes were negative, and the residual disease was ≥2 cm, the patient would escape chemotherapy and simply continue 5 years of postoperative letrozole therapy.

From a statistical point of view, the trial would be powered for equivalent outcomes on the two treatment arms: that is, despite the use of preoperative letrozole and a reduction in chemotherapy administration on the experimental arm, the two arms would have similar relapse-free and overall survival statistics. If this was the case, a clear improvement in clinical management will have been made that would be comparable with the validation of breast-conserving surgery, namely, an improvement in the quality of life (in this case the reduced administration of chemotherapy) without compromising long-term outcome. If this study was a success, new clinical study designs could follow, in which neoadjuvant endocrine therapy becomes the new standard, and the value of chemotherapy in more finely defined subsets or a strategy of switching to alternative endocrine agents or biological therapies could be evaluated. However, we should resist the temptation to build in secondary randomizations (i.e., depending on postneoadjuvant status) until the initial study has established the molecular and clinical basis on which these clinical experiments would be based.
Summary

Besides establishing a low-toxicity neoadjuvant approach for older patients with ER+ breast cancer, the clinical significance of neoadjuvant endocrine therapy lies in the opportunity to predict long-term endocrine therapy outcomes in early-stage breast cancer. The focus on clinical, radiological, and pathological response will increasingly be redirected toward molecular end points and the use of predictive biomarkers to determine treatment. For example, one can easily imagine that tumor proliferation rates or gene expression changes after neoadjuvant endocrine therapy could be powerful predictors of the failure of adjuvant therapy. Neoadjuvant endocrine therapy for breast cancer is an intriguing concept that is beginning to gain momentum as a way to address some of the most fundamental questions concerning the nature and treatment of breast cancer.

Open Discussion

Dr. Paul Goss: You argue that the assessment of clinical response isn’t very good by either clinical measurement or mammography. We all agree with that. Then you have to remember that it’s not inconceivable that what you’re testing in those 40% of patients who did not show a response is the effect on long-term survival of a delay in breast cancer surgery of 4 months. You’re testing a clinical question: does delaying breast cancer surgery for 4 months prejudice the survival of breast cancer patients? And that’s something that I think has to come out in a consent form for this kind of a trial.

Dr. Matthew Ellis: You don’t know that the ones who do not show a clinical response aren’t deriving systemic benefit from the treatment. Ultimately, this concern will have to be addressed in a randomized control setting. The setting I was thinking about is preoperative chemotherapy versus preoperative hormones. The ones who have responded well to hormones get no chemotherapy with continued endocrine therapy, and the ones who didn’t respond, by whatever criteria you decide, go on to get chemotherapy plus hormones. Because the margin of benefit for chemotherapy in this population is relatively small, if you come up with a strategy that tells you which patients don’t need chemotherapy, that actually would be a big advance in breast cancer management.

References

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