The Fifth International Conference on Recent Advances and Future Directions in Endocrine Manipulation of Breast Cancer, co-chaired by Steven Come, M.D., and Aman Buzdar, M.D., was held in Cambridge, Massachusetts, June 13-14, 2005.

The conference was organized with the objective of analyzing recent advances in basic, translational, and clinical research relating to endocrine manipulation of breast cancer, and examining the implications of these findings both for patient management and for future research. Conference attendees were selected based on their contributions to the basic or clinical understanding of breast cancer and included internationally recognized researchers in the fields of molecular biology, pathology, pharmacology, epidemiology, and medical oncology.

The conference, which combined brief scientific reports with extended periods of open discussion, focused on the following issues:

- The complexity of interactions between the estrogen receptor (ER) and other subcellular pathways, highlighting the role of ER coregulatory proteins and of adaptor and chaperone proteins which link growth factor signaling and nongenomic ER function.
- The significance of quantitative ER level, progesterone receptor (PR) status, and tumor genome expression profiling in selecting therapy and/or predicting response to treatment.
- The correlation between molecular markers and tumor response in neoadjuvant studies of endocrine therapies.
- Reviews of recent data both from initial reports and ongoing follow-up of the major adjuvant endocrine clinical trials.

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**Basic Science**

**Mechanisms of resistance to endocrine therapy.** Multiple potential mechanisms for resistance to tamoxifen have emerged. Among these, there is increasing evidence to suggest that the nongenomic activity of the ER may play a role in resistance to tamoxifen. Recent data suggest that functional ER activity in the cytoplasm is dependent on the epidermal growth factor receptor (EGFR) pathway, which can phosphorylate the ER in a ligand-independent fashion in vivo. Preclinical studies, inhibition of EGFR signaling with gefitinib restores sensitivity to tamoxifen. Human EGFR-2 (HER2) overexpression, leading to increased signaling in this growth factor pathway and cross-talk with the ER, has also been implicated in tamoxifen resistance. In one small study, among tumors that recurred during tamoxifen treatment, ~10% of those that were initially HER2 negative acquired HER2 overexpression.

Less is known about resistance to aromatase inhibitors but it now seems that the hypersensitivity to estrogen observed in estrogen-deprived cultured breast cancer cells is also dependent on an increase in growth factor signaling. HER2 overexpression cross-talking with the ER and its coactivator proteins can induce resistance to aromatase inhibitors in animal models. Moreover, increased signaling in the EGFR pathway may be sufficient for resistance to aromatase inhibitors or tamoxifen even if EGFR and HER2 expression levels are not found to be increased by the techniques presently employed to measure them. A question to be answered is whether inhibitors of the EGFR/HER2 pathway might delay resistance to selective estrogen receptor modulators and aromatase inhibitors in patients who do not overexpress these growth factor receptors. Indeed, it is possible that inhibition in that setting might be more effective than in patients who already have biochemically overt increased growth factor signaling.

With our expanding knowledge of the complexity and redundancy of cellular pathways, including the roles of receptor coregulatory proteins, adaptor proteins, and chaperone proteins, we can no longer accept a simple receptor-centered approach.
explanation of hormone resistance. Further, in cytoplasmic and nongenomic signaling, the signal can proceed in many directions and numerous pathways can be activated simultaneously. This complexity presents a great challenge to researchers seeking to discover unifying themes and ultimately therapeutic targets.

**Translational Science**

The presurgical setting affords an exceptionally valuable opportunity to study therapeutic agents and combinations. The identification of reliable molecular predictors of response and markers of resistance has the potential to greatly facilitate both our understanding of endocrine therapy and the clinical trials process. Given the large number of potential agents and combinations that could be studied and the high cost of clinical trials, the ability to screen and prioritize approaches could save valuable time, effort, and cost. For example, the neoadjuvant IMPACT trial, which involved a small number of patients and only 12 weeks of treatment, correctly predicted that combination tamoxifen/anastrozole therapy would offer no benefit over tamoxifen. Had the IMPACT study been completed first, the 3,000-plus patient multiyear arm of combined tamoxifen and anastrozole in the adjuvant ATAC trial might not have been done.

The approach of linking presurgical studies to subsequent therapeutic trials could be extraordinarily valuable as we attempt to combine other biologically targeted therapies with endocrine therapy. An ability to measure putative targets and to determine the extent to which they are affected by therapy will be critical both in defining trial design and in interpreting results. Change in the antiproliferation marker Ki-67, used in the IMPACT biomarker study, has shown a significant, although modest, correlation with clinical outcome. Recent data from genome-wide profiling studies have the potential for identifying global indices of endocrine response and resistance. Methodologies are now available to extract mRNAs species from archival paraffin blocks and to interrogate gene expression levels in these materials with high efficiency. These approaches can be applied not only to new studies but also to archival materials from ongoing or completed trials wherein clinical correlations are already available. A similar approach of molecular and genomic analysis of paired specimens taken before endocrine treatment and at the time of progression in patients with metastatic breast cancer will also advance our understanding of resistance mechanisms. Observations made in this setting can be translated to the presurgical study of women with early breast cancer.

**Clinical Update: Adjuvant Endocrine Therapy**

**Premenopausal and perimenopausal women.** In premenopausal patients, tamoxifen remains the primary endocrine agent available for adjuvant therapy. Aromatase inhibitors are not employed as monotherapy in premenopausal women as the first- and second-generation agents could not suppress estrogen production in the ovaries and the current third-generation agents have not been tested. In addition, the use of aromatase inhibitors alone has been associated with ovarian follicle production related to a reflex increase in gonadotropin secretion. In premenopausal women, the role of combined tamoxifen and ovarian function suppression versus tamoxifen alone and the effectiveness of ovarian function suppression plus an aromatase inhibitor are being evaluated in the ongoing Suppression of Ovarian Function Trial and Tamoxifen and Exemestane Trial studies.

Although it is essential to differentiate premenopausal and postmenopausal patients in selecting endocrine therapies, in clinical practice menopause status is not always easily ascertained. This is particularly the case for women who are premenopausal before receiving adjuvant chemotherapy but become amenorrheic during treatment. Studies have shown that up to 20% of women who are not having menstrual cycles during the first 6 to 12 months after chemotherapy nevertheless have intact ovarian function. Further, even women with postmenopausal levels of follicle-stimulating hormone and estradiol soon after chemotherapy may recover menses over time. A frequent additional complicating factor is the lack of reliability of measuring these variables in women who are taking tamoxifen. In this setting, it would be prudent to confirm that a patient is biochemically postmenopausal by determining estradiol and follicle-stimulating hormone levels before initiation of an aromatase inhibitor and to follow the patient clinically for recurrence of menses. If menses recur in this situation, either a switch from an aromatase inhibitor to tamoxifen or the addition of ovarian function suppression would be an appropriate option.

**Postmenopausal women.** As initial adjuvant therapy in postmenopausal women with hormone receptor–positive disease, nonsteroidal aromatase inhibitors are more effective than tamoxifen in reducing the risk of cancer recurrence. This has been shown both for anastrozole in the ATAC trial, now mature with a median follow-up of 68 months and only 8% of patients still on therapy. This finding was confirmed recently in the initial report of the Breast International Group 1-98 trial, which compares 5 years of letrozole to 5 years of tamoxifen as initial endocrine therapy as well as the sequences of 2 years of tamoxifen followed by 3 years of letrozole and the reverse in over 8,000 postmenopausal women with hormone receptor–positive breast cancer.

Three reports (the Intergroup Exemestane Study, the combined ABCSG 8 and ARNO93 trial, and the IDEA trial) have shown that using a nonsteroidal (anastrozole) or steroidal (exemestane) aromatase inhibitor following 2 to 3 years of tamoxifen is associated with a reduction in risk of recurrence compared with completing a 5-year course of tamoxifen. This “switching” strategy is now advocated for women who have chosen tamoxifen as their initial adjuvant therapy.

It is unknown at this time whether initial therapy with an aromatase inhibitor or some sequential use of tamoxifen and an aromatase inhibitor will be the best strategy. The American Society of Clinical Oncology Technology Assessment Panel, as well as the St Gallen Consensus Conference, has endorsed both approaches. The mature results of ongoing studies will be needed to determine if there is a single best strategy. It is also possible that different strategies will be appropriate for different patients depending on both tumor and patient characteristics.

In women who receive 5 years of tamoxifen as their adjuvant therapy, there is a stage-dependent residual risk of recurrence that persists over at least the following decade. Treatment with an aromatase inhibitor after completion of tamoxifen therapy can further reduce the risk of breast cancer recurrence as shown in two studies of extended adjuvant therapy with aromatase...
inhibitors following 5 years of tamoxifen, the large MA.17 trial and the much smaller ABCSG 6a study. The decision about extended adjuvant therapy should be based on an estimate of a woman’s residual risk following tamoxifen. The MA.17 trial is also of great value because it compares the safety and tolerability of an aromatase inhibitor to a placebo rather than to tamoxifen as in the initial adjuvant and switching trials. Further, the rerandomization of women who complete 5 years of letrozole in this trial to an additional 5 years of therapy (versus placebo) will help to define the optimal duration of aromatase inhibitor therapy and to define the carryover effect of the initial 5 years of treatment. At present and going forward, it is expected that few postmenopausal women appropriate for adjuvant endocrine therapy will first receive an aromatase inhibitor 5 years after diagnosis. The positive results in both the initial therapy and switching trials will likely lead to the earlier use of these agents.

Whereas both switching studies and extended adjuvant therapy studies have shown benefit for an aromatase inhibitor after tamoxifen, the combination arm in ATAC clearly showed that there is no present role for concurrent use of a nonsteroidal aromatase inhibitor with tamoxifen. The combination of the pure antiestrogen fulvestrant, which has no known estrogen agonist activity, may have a role in combination with an aromatase inhibitor. The initial therapy trials—ATAC and Breast International Group 1-98 trial have two sequence arms in which patients were randomized at the outset to receive an initial 2 years of tamoxifen followed by letrozole or the reverse sequence. However, the sequence arms are relatively small (∼1,500 patients in each), leaving the trial potentially underpowered to compare monotherapy with letrozole to sequential treatment. Further, these data will not be available until 2008.

In the absence of direct clinical trial data, models have been created to address this issue. These have been based on differing assumptions and end points. In a model focusing on years of life lost with an emphasis on early years, aromatase inhibitor monotherapy is favored. Two other models favor the sequential therapy for patients with ER-positive, PR-positive tumors although the potential advantage for that approach does not emerge until at least 7 years after diagnosis. It must be stressed that the conclusions of models are hypothesis-generating and ultimately require support by data from randomized clinical trials.

At present, it is clear from the existing trial data that during the first 2 to 3 years of adjuvant endocrine therapy, there are fewer recurrence events and fewer adverse events when the initial therapy is an aromatase inhibitor rather than tamoxifen. Whether the longer-term outcome is best with this approach cannot be resolved without direct clinical data comparing planned sequential therapy to aromatase inhibitor monotherapy. Further, if an advantage is ultimately established for sequential treatment, the optimal duration of tamoxifen will need to be defined. Thus, additional large clinical trials will likely be necessary to address these issues as well as the optimal duration of aromatase inhibitor therapy.

It is noteworthy, however, that there are several ongoing large randomized studies of hormonal therapies with or without signaling inhibitors in postmenopausal women with ER-positive metastatic disease, in which an aromatase inhibitor alone is used as the “control” arm. If these trials in metastatic disease are positive and sequencing hormonal therapies are found to be superior to aromatase inhibitors alone in the adjuvant setting, this may raise some questions about the prompt implementation of trials using aromatase inhibitors (alone) plus signaling inhibitors in the adjuvant setting.

Tumor phenotype and behavior. Emerging evidence, not all of it consistent, suggests that PR status may distinguish populations of patients with differential levels of benefit from the aromatase inhibitors. ER-positive, PR-negative tumors seem to have distinct clinical and biological characteristics compared with the ER-positive, PR-positive tumors. Relative to tumors positive for both hormone receptors, ER-positive, PR-negative breast cancers often overexpress EGFR and HER2. The clinical relevance of these observations is that ER-negative, PR-negative tumors are known to be relatively resistant to selective estrogen receptor modulator therapy, presumably due to increased growth factor signaling. A recent retrospective analysis of this

**Unresolved Issues and Research Priorities**

**Future for tamoxifen.** Current evidence suggests that the nonsteroidal aromatase inhibitors anastrozole and letrozole are slightly superior to tamoxifen in each of the randomized trials. It remains unclear, however, whether this small advantage is equally experienced by all patients or whether the overall results reflect in part or in total a subset of patients for whom there is a disproportionate benefit favoring an aromatase inhibitor. The agonistic effects of tamoxifen have been shown to be enhanced in oncogene-overexpressing ER-positive cancers. Therefore, especially in tumors with high EGFR and/or HER2 levels, a hormonal deprivation approach with an aromatase inhibitor might be preferable over tamoxifen. At present, based on both clinical trials and on preclinical models, there is no subpopulation of patients in whom an aromatase inhibitor would be inferior to tamoxifen in terms of efficacy. However, it remains a possibility that such patients may be identified, and clinical decisions need to be made based on both efficacy and potential toxicity for the individual patient.

The superiority of aromatase inhibitors nevertheless leaves open the question on whether there is any advantage to the sequence of tamoxifen followed by an aromatase inhibitor (or the reverse) rather than monotherapy with an aromatase inhibitor. The initial therapy trials—ATAC and Breast International Group 1-98—cannot be compared directly to the switching trials—Intergroup Exemestane Study, ABCSG 8/ARNO95, and ITAC—because the populations in the latter are “enriched” for endocrine sensitivity as the patients included are all recurrence-free following at least 2 years of initial tamoxifen. Based on exploratory unplanned subset analysis from the ATAC trial, it seems that tumors which express both ER and PR may be almost comparably responsive to tamoxifen and to aromatase inhibitor. In contrast, those ER-positive tumors which do not express PR, perhaps a surrogate for increased growth factor signaling, respond much better to an aromatase inhibitor. At present, these data, although preliminary, do suggest that women with tumors that are ER positive but PR negative should receive an aromatase inhibitor from the outset.

For most postmenopausal women with hormone receptor–positive tumors, however, both the ER and PR are expressed. For these patients, there is some controversy on the best treatment strategy. The Breast International Group 1-98 trial has two sequence arms in which patients were randomized at the outset to receive an initial 2 years of tamoxifen followed by letrozole or the reverse sequence. However, the sequence arms are relatively small (∼1,500 patients in each), leaving the trial potentially underpowered to compare monotherapy with letrozole to sequential treatment. Further, these data will not be available until 2008.
subgroup in the ATAC trial, discussed at greater length elsewhere in these proceedings by Lee, suggests that although these patients are at an overall increased risk of recurrence, their tumors seem to be markedly more sensitive to aromatase inhibitors than to tamoxifen. However, this retrospective subgroup analysis has not been confirmed by the preliminary analysis of the Breast International Group 1-98 trial, and central analysis of hormone receptor status is being done for both ATAC and Breast International Group 1-98 trials. In evaluating the conflicting evidence, there are methodologic issues with how PR status is measured, and, in fact, in many trials PR status has not been consistently ascertained and/or reported.

Safety and quality-of-life issues in choosing therapy. Considerable safety and tolerability data are now available from the large adjuvant endocrine therapy trials, and more data will be forthcoming over the next few years. The safety profile of aromatase inhibitors has been established, with follow-up data out to a median of 68 months for anastrozole in the ATAC trial. Although these agents seem, as a class, to be acceptably safe compared with tamoxifen, bone health, lipid status, and the slight increase in cardiovascular events recorded in some, but not all, trials will require further investigation.

There is also a substantial amount of quality-of-life data emerging from these trials. Overall, adjuvant endocrine therapy with tamoxifen or with an aromatase inhibitor seems to be acceptable to most patients with some quality-of-life studies showing improvement over time on therapy. The aromatase inhibitors dramatically lower estrogen levels and concerns about the effects on sexual function remain. In the ATAC quality-of-life studies, now updated to 5 years, there is a statistically significant increase in vaginal dryness, dyspareunia, and loss of sexual interest with aromatase inhibitors versus tamoxifen. Although many clinicians employ vaginal estrogen preparations to ameliorate some of these symptoms, the effect of vaginal estrogen administration on the efficacy of ongoing aromatase inhibitor therapy has not been investigated.

Continuing attention to both safety and quality-of-life issues will be very important, particularly as many women are now being offered prolonged endocrine therapy. Because the efficacy differences between adjuvant endocrine therapeutic strategies seem to be relatively small, emerging differences about safety and tolerability will be a significant factor in shaping clinical choices. These issues will affect both decisions about the use of tamoxifen versus aromatase inhibitors and potentially choices among the available third-generation aromatase inhibitors.

Challenges in future research. The study of ER mRNA in the National Surgical Adjuvant Breast and Bowel Project B-14 trial (placebo versus tamoxifen) showed that there is a linear correlation between the level of target molecule (ER) and the level of clinical benefit achieved with the targeted therapy (tamoxifen). This paradigm illustrates how important it will be in ongoing clinical trials to precisely and consistently measure therapeutic targets. This will be critical in our attempt to understand clinical outcomes.

The task of delineating the many pathways potentially contributing to resistance is rendered more difficult by the paucity of preclinical models of these pathways. More modeling studies are needed to explore potential additive or synergistic effects of combinations of endocrine therapy and molecular targeted agents. A firm biological rationale and a rational development plan for clinical investigations of these novel combinations will be essential to the success of clinical trials. Ultimately, however, molecular data from human breast cancer are essential. Therefore, a concerted effort should be made to obtain specimens at the time of tumor recurrence/progression and to interrogate this material for changes in gene or protein expression associated with tumor resistance. This approach has the potential to provide additional insights into the mechanisms of resistance to endocrine therapy as well as the optimal approaches to its management.

Experimental and clinical studies are now exploring combinations of novel molecular targeted therapies with endocrine therapies. The rationale for these combinations is to overcome or prevent endocrine resistance that arises due to cross-talk with growth-promoting and/or antiapoptotic pathways. Early clinical and biomarker data are now available with several such agents, as monotherapy and/or combination therapy, including the EGFR tyrosine kinase inhibitors gefitinib and erlotinib, the dual EGFR/HER2 tyrosine kinase inhibitor lapatinib, and the mTOR antagonist temsirolimus. A number of phase II/III trials have been undertaken with gefitinib in combination with tamoxifen, fulvestrant, or an aromatase inhibitor. Phase III trials are also under way to investigate the combinations of letrozole/lapatinib and fulvestrant/lapatinib in metastatic breast cancer. In investigating the potential clinical benefit of these combination endocrine and novel targeted therapies, selection of patients who express the intended targets is important, and thus, correlative biomarker studies will be critical.

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