

Proceedings of the Fourth International Conference on Recent Advances and Future Directions in Endocrine Manipulation of Breast Cancer: Conference Summary Statement

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The Fourth International Conference on Recent Advances and Future Directions in Endocrine Manipulation of Breast Cancer, co-chaired by Steven Come, MD, and Aman Buzdar, MD, was held in Cambridge, MA, July 21-22, 2004.

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, pharmacology, epidemiology, and medical oncology.

Presented at the Fourth International Conference on Recent Advances and Future Directions in Endocrine Manipulation of Breast Cancer, July 21-22, 2004, Cambridge, Massachusetts.

Grant support: The symposium and publication of these proceedings were made possible by unrestricted educational grants from AstraZeneca Pharmaceuticals, Novartis Pharmaceuticals, Pfizer Oncology, and Taiho Pharmaceuticals.

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

- The biology of the estrogen receptor (ER) and how ligand-dependent conformational changes in the receptor and receptor down-regulation present new therapeutic opportunities.
- The mechanisms of resistance to both tamoxifen and the aromatase inhibitors.
- The scientific rationale, preclinical evidence, and clinical experience to date supporting the use of combination therapies to improve efficacy and delay resistance to endocrine-based treatment.
- Current understanding of the biology of transforming growth factor (TGF)- β and type 1 insulin-like growth factor (IGF-I) and their potential as therapeutic targets.
- Emerging data on aromatase inhibitors in early breast cancer: implications for clinical practice today.
- New drug development: preclinical and early clinical findings for the steroidal antiestrogen TAS-108.
- Aromatase inhibitors in breast cancer prevention.
- The protective effect of early pregnancy on the breast and the possible application of biological and genomic observations in this model to an alternative prevention strategy.
- Priorities for translational and clinical research.

At the conclusion of the conference, the faculty convened to formulate the following summary statement.

BASIC SCIENCE

Mechanisms of Resistance to Endocrine Therapy

Findings in both preclinical and clinical studies suggest that the mechanisms of resistance to selective estrogen receptor modulators (SERMs) and aromatase inhibitors are at least partially distinct. When bound to the ER, estrogen induces a conformational change in the receptor that allows the recruitment of coactivators and facilitates transcription. In contrast, the binding of SERMs such as tamoxifen to the ER results in a different receptor conformation. In breast tissue, this normally favors the recruitment of corepressors, which inhibit transcriptional activity. Thus, the bound ligand determines the receptor conformation, and that, in turn, may dictate the preference for coactivators versus corepressors. The availability of these coregulatory proteins in a specific tissue also likely impacts this process. For example, although tamoxifen primarily displays antagonist properties in the breast, its weak agonist activity is enhanced in the presence of high levels of coactivators such as AIB1 (SRC3).

There is increasing recognition that growth factor pathways play a central role in resistance to endocrine therapy.

Although activation of the epidermal growth factor receptor (EGFR)/HER-2 signaling pathway directly promotes cell proliferation, invasion, and motility while inhibiting apoptosis, there is also crosstalk between this pathway and the ER. This interaction may take place in or near the cell membrane where a small quantity of ER can directly and rapidly activate growth factor receptors such as EGFR, HER-2, and IGF-IR. In preclinical models of tamoxifen resistance, overexpression of HER-2 results in phosphorylation and activation of the ER and of coactivators such as AIB1. In this setting, tamoxifen, like estrogen, has a growth-stimulatory effect. This is not only the result of an increased agonist effect on the ER but also because in a reciprocal manner, both estrogen and tamoxifen cause phosphorylation and activation of growth factor signaling intermediates. This observation is supported by clinical data demonstrating a relative lack of efficacy of tamoxifen in tumors that overexpress HER-2 or the combination of HER-2 and AIB1.

When breast cancer cells are grown under long-term estrogen deprivation, a model which simulates aromatase inhibitor therapy in postmenopausal women, an adaptive hypersensitivity to low levels of estrogen emerges. Although both long-term estrogen deprivation cells and xenograft tumor models exposed to aromatase inhibitors display some initial up-regulation of the ER, it appears that increased growth factor pathway signaling, particularly in the MAPK cascade, is more critical to the process of adaptation and tumor resistance. In ER-positive/HER-2-positive models treated with estrogen deprivation, crosstalk between the ER and the growth factor cascade is evident. Initially, removal of estrogen produces a reduction in MAPK signaling. As resistance develops, there is an increase in growth factor signaling, which is associated with a reversible reduction in ER and ER-regulated genes such as the progesterone receptor (PR) gene. Abrogation of growth factor signaling can restore sensitivity to endocrine therapy, and this is associated with the reappearance of ER and estrogen-dependent transcription.

In the presence of increased growth factor signaling, there is a theoretical advantage for an aromatase inhibitor versus tamoxifen, and this appears supported in preliminary clinical data from patients who are either ER-positive/HER-2-positive or ER-positive/PR-negative. Although growth factor pathway activation has a negative effect on response to both agents, the aromatase inhibitor avoids the growth-stimulatory effect of tamoxifen in this setting. Further, in aromatase-transfected MCF7 xenograft models, the combination of letrozole and ER down-regulation with fulvestrant delays progression compared to letrozole alone, perhaps by more effectively reducing crosstalk between the ER and growth factor pathways.

TRANSLATIONAL SCIENCE

Addressing Crosstalk in Clinical Trials

These preclinical observations indicate that interfering with crosstalk by simultaneously targeting both the ER and other cellular pathways may be an effective therapeutic strategy. Several clinical trials are underway exploring combinations of antiestrogens or aromatase inhibitors with new agents which inhibit growth factor signaling, mTOR, or farnesyl transferase. In such

trials, patient selection would be expected to have a major impact on results. Identification of patients who have up-regulation of the pathways that are the intended targets may be essential for therapeutic benefit. However, with the exception of patients who are ER-positive and overexpress HER-2, as yet there is no well-developed approach to ensure that patients entering trials with targeted biologic therapies actually have tumors which depend on the pathways being targeted. Thus, there is a significant danger that potentially useful strategies could be discarded because they are evaluated in the wrong patient population. To the extent that these trials will first be done in the traditional metastatic disease setting, an increased emphasis on acquiring tissue specimens to assess molecular biology and gene expression profiles before and after therapy will be important. Correlating this biological data with response data should aid in enriching patient populations in subsequent trials of molecularly targeted agents and might ultimately allow clinicians to individualize therapy.

Biological and Clinical Correlations in the Neoadjuvant Setting

Neoadjuvant trials, where tissue is easily accessible pretherapy and posttherapy, should be considered in parallel with traditional metastatic disease and adjuvant therapy trials in evaluating novel therapies in order to correlate clinical and pathologic data with molecular data. Recent findings from the IMPACT trial have questioned the feasibility of using clinical response as an endpoint in the neoadjuvant setting, given the slow regression of tumors exposed to endocrine therapy: biological response may be a more sensitive short-term indicator of ultimate clinical response to a novel therapy or combination. However, further work must be done to validate these correlations. Neoadjuvant studies with biological endpoints pretherapy and posttherapy could greatly contribute to our understanding of resistance to endocrine therapy; moreover, studies in this setting could facilitate the evaluation of different sequencing and dosing regimens for combination therapy with endocrine agents and signal transduction inhibitors. Such studies should employ dual endpoints, combining biological markers to verify effects on the putative target with cellular endpoints such as the cell proliferation marker Ki-67 and the TUNEL assay of apoptosis, to verify that an effect on the biologic target is associated with a change in tumor growth. Functional imaging by positron emission tomography or magnetic resonance imaging could potentially contribute to this evaluation. More work must be done to determine if neoadjuvant endocrine studies may be used as surrogates for postoperative adjuvant therapy studies and thus reduce the substantial outlays of resources required for these large-scale trials.

ENDOCRINE THERAPY: CLINICAL UPDATE

Adjuvant Therapy

Regardless of the age of the patient, endocrine adjuvant therapy offers substantial potential for benefit in terms of reduction in risks of recurrent breast cancer and of death in women with early stage disease whose tumor is positive for ER and/or PR. Tamoxifen has been the standard of care for several decades for both premenopausal and postmenopausal women. However, recent data from large, well-conducted, randomized,

double-blind clinical trials have established the value of the third-generation aromatase inhibitors, anastrozole, exemestane, and letrozole, in postmenopausal women with early breast cancer. These three trials, the Arimidex and Tamoxifen Alone and in Combination (ATAC) trial, the International Exemestane Study, and MA.17, examined the use of an aromatase inhibitor in three different settings. ATAC evaluated anastrozole versus tamoxifen for 5 years as initial treatment; the International Exemestane Study evaluated exemestane versus tamoxifen following 2 to 3 years of tamoxifen for a total of 5 years of endocrine adjuvant treatment; and MA.17 compared a planned 5 years of letrozole versus placebo in women who all had 4.5 to 6 years of tamoxifen. In all three trials, the use of the aromatase inhibitor was associated with a statistically significant improvement in disease-free survival. Only one study, MA.17, has demonstrated a survival advantage, and only in the node-positive subset. A constant finding has been a different toxicity pattern, with the aromatase inhibitor being associated with a lower incidence of thromboembolic events and endometrial cancer but a higher incidence of musculoskeletal complaints and fractures relative to tamoxifen. The evidence relating to the aromatase inhibitors pertains only to postmenopausal women. In premenopausal women, tamoxifen remains the standard for endocrine treatment. The aromatase inhibitors are being studied in conjunction with ovarian function suppression in the Suppression of Ovarian Function Trial (SOFT) and in the Tamoxifen and Exemestane Trial (TEXT), but their use in this setting remains investigational.

Based on the available evidence from the randomized clinical trials noted above, the following recommendations can be made for postmenopausal women with early stage (stages I and II) breast cancer.

- Given the growing body of evidence correlating treatment response to distinct patient subsets, clinicians should ascertain receptor status, ER, PR, and HER-2.
- All women with ER-positive and/or PR-positive tumors should receive adjuvant endocrine therapy.
- As initial therapy, an aromatase inhibitor (anastrozole) is a reasonable choice based on improved disease-free survival and a lower incidence of thromboembolic events and endometrial cancer relative to tamoxifen. Tamoxifen remains an option, particularly when there is concern about the risk of fractures or about the relative lack of information regarding long-term treatment and associated toxicities with anastrozole, especially in patients with ER-positive and PR-positive tumors where, in an exploratory analysis, the superiority of the aromatase inhibitor was not as pronounced as in patients with ER-positive and PR-negative tumors.
- In women who have received 2 to 3 years of tamoxifen, a switch to an aromatase inhibitor (exemestane) is reasonable based on an improved disease-free survival with this strategy, compared with continuation of tamoxifen for 5 years.
- In women completing 5 years of tamoxifen, extended adjuvant therapy with an aromatase inhibitor (letrozole) should be considered, taking into account the residual risk of recurrence and thus potential benefit, as well as

the potential risk of bone and musculoskeletal effects with long-term aromatase inhibitor therapy.

- Although the efficacy reported for specific aromatase inhibitors in different settings may be a class effect, this has not been demonstrated; therefore, the aromatase inhibitor chosen should be the one studied in the clinical setting most similar to that of the individual patient.
- Duration of therapy with the respective aromatase inhibitor should be that employed in the clinical trials, as this represents the extent of knowledge.
- Given the potential for increased risk of fracture with aromatase inhibitor therapy, bone mineral density testing should be done prior to initiation of an aromatase inhibitor in the adjuvant setting, with appropriate treatment utilized for osteopenia or osteoporosis based on existing guidelines. Clinicians should be aware of the apparent negative interactions between aromatase inhibitors and SERMs such as raloxifene.
- Patients should be fully informed of the potential for benefit and the adverse effects of therapy with aromatase inhibitors and that issues such as optimal duration of treatment and long-term adverse effects are still under study.

Clinicians should be aware as well of the unanswered questions regarding the management of women newly diagnosed with breast cancer, primarily concerning sequencing and duration of adjuvant therapy. It is not known, for example, whether it is better to start with an aromatase inhibitor immediately rather than tamoxifen, or whether there may be a benefit from “priming” the tumor with tamoxifen. If the clinician elects to treat with tamoxifen first, when it is most likely to be effective, the optimal duration of tamoxifen treatment before the switch to aromatase inhibitor therapy has not been established. It is likely that the answers will differ for differing subsets of disease, but there are currently few data on which to base these decisions. Some preliminary evidence suggests that the optimal initial treatment for HER-2-positive disease might be an aromatase inhibitor rather than a SERM, whereas patients with ER-positive and PR-positive tumors might be optimally treated with the sequence of tamoxifen for 3 to 5 years followed by aromatase inhibitor therapy. Finally, and most crucially, the optimal duration of aromatase inhibitor therapy is unknown, as are the long-term toxicities of prolonged aromatase inhibitor therapy.

Sequencing of Therapy in Advanced Disease

Given that an increasing number of women are receiving an aromatase inhibitor as initial therapy, the standard of care for advanced disease and the sequencing of therapies are issues that will need to be revisited in clinical trials and in the clinic. The preferred second-line therapy for women with ER-positive tumors who have developed resistance to initial aromatase inhibitor therapy has not been established. In particular, it is not clear whether tamoxifen is effective following an aromatase inhibitor. Until the Breast International Group/Femara-Tamoxifen (BIG-FEMTA) trial reports, there are no randomized trial data that directly address the issue of whether it is better to give an aromatase inhibitor first or to give tamoxifen followed by

aromatase inhibitor. A number of trials are now examining the effects of sequential versus combined endocrine agents. At this time, however, there are no new data to venture beyond the summary made at the conclusion of the 2003 conference, namely:

- For postmenopausal women presumed to be tamoxifen-sensitive (either no prior tamoxifen or > 1 year between cessation of tamoxifen and disease progression) nonsteroidal aromatase inhibitors are preferable to resumed tamoxifen treatment.
- For postmenopausal women considered to be tamoxifen-resistant (≤ 1 year between cessation of adjuvant tamoxifen and disease progression), steroidal or nonsteroidal aromatase inhibitor or fulvestrant are all reasonable options based on available data.
- At this time, it is unknown whether there is an advantage for the use of fulvestrant before versus after use of aromatase inhibitors.
- For women who have progressed on nonsteroidal aromatase inhibitor therapy, a steroidal aromatase inhibitor, fulvestrant, tamoxifen, and megestrol acetate are all options; clinical response has also been reported for pharmacologic doses of estrogen following failure of an aromatase inhibitor.

Given the many unanswered questions regarding sequencing of therapy, it is entirely appropriate for the physician to consider enrollment of patients with advanced disease into a clinical trial that includes any of these agents.

RISK AND PREVENTION OF BREAST CANCER

Fundamentally, estrogens promote breast cancer, presumably by stimulating cell proliferation, and estrogen metabolites may also exert a direct, weak genotoxic effect on breast tissue. Although there are data from the Women's Health Initiative study showing a slight reduction in breast cancer risk with hormone replacement therapy, the high dropout rate in this study raises concerns of selectivity; the breadth of evidence, in fact, suggests that estrogen alone can increase the risk of breast cancer. Although the data are limited, continuous combined and sequential hormone replacement therapy appear to have comparable effects in increasing risk. The evidence also suggests that a relatively short-term exposure of 5 years of estrogen plus progestin is sufficient to increase the risk of breast cancer, just as in the P1 study, 5 years of tamoxifen therapy will significantly reduce risk.

Although tamoxifen has demonstrated efficacy in reducing the incidence of breast cancer in women at increased risk, many eligible women are reluctant to take tamoxifen prophylactically, primarily from concern over the risk of endometrial cancer and thromboembolism. Accordingly, there has been interest in studying other agents in the prevention setting in the hopes that they may offer comparable benefits in preventing breast cancer with a more acceptable toxicity profile. Data from adjuvant trials have shown a reduction in contralateral breast cancer with aromatase inhibitor therapy that appears superior to the effect of tamoxifen. Prevention trials with aromatase inhibitors are underway but are not yet mature. Long-term bone, lipid, and

quality-of-life data are being collected. The optimal duration of prevention therapy—limited (e.g., 5 years) versus continuous—also remains to be defined. In counseling women at high-risk about breast cancer prevention options, clinicians should also note the association of body mass index and plasma estrogen levels, which may support optimization of weight as one helpful lifestyle intervention.

Prevention efforts to date have focused on the adult woman, but both epidemiologic data and animal models of the developing breast confirm that an early first full-term pregnancy affords long-term protection against breast cancer. In the animal model, pregnancy induces a specific and persistent genomic signature that is not present in the nulliparous breast. Acquisition of this signature could be a potentially useful biological endpoint in evaluating a prevention strategy. In this model, this signature can be induced by a short exposure to human chorionic gonadotropin, providing one testable alternative to long-term use of SERMs or aromatase inhibitors.

UNRESOLVED ISSUES AND RESEARCH PRIORITIES

As more women are receiving an aromatase inhibitor in the adjuvant setting, the optimal duration of therapy and the long-term toxicities of prolonged treatment are issues that need more extensive evaluation. Further data are also needed to guide selection of therapy when resistance to an aromatase inhibitor develops. More research is needed to confirm the observation from the unplanned subset analyses in the ATAC trial which suggests that the superior efficacy of anastrozole compared to tamoxifen is particularly pronounced in women with PR-negative tumors.

Despite the rising use of and enthusiasm for aromatase inhibitors, a case can still be made for SERMs, which at present is tamoxifen, and for the identification of new agents in this class. Aromatase inhibitors do not remove all ligand, leaving an intact and potentially transcriptionally active ER. There is potential to develop a SERM which induces a conformational change in the ER that will eliminate the recruitment of coactivators. Further, preclinical observations support the efficacy of a SERM in the setting of increased growth factor signaling when used in combination with a growth factor signaling inhibitor such as gefitinib. For long-term use as in the adjuvant or prevention settings, avoidance of long-term estrogen deprivation may have important advantages.

There is extensive preclinical research of great interest and promise. The evaluation of these findings in the clinic can be greatly accelerated by the development and validation of biologic markers that are predictive of clinical efficacy. Genomics and proteomics should be increasingly incorporated into neoadjuvant or short-term presurgical studies to better understand issues of patient selection and resistance mechanisms for specific therapies and combinations.

ACKNOWLEDGMENTS

Editorial assistance and CME Sponsorship were provided by InforMEDical Communications, Inc., Carlisle, MA, USA.