Proceedings of the First International Conference on Recent Advances and Future Directions in Endocrine Therapy for Breast Cancer: Summary Consensus Statement

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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 medical oncology, molecular biology, pharmacology, and pathology.

Introduction  
The conference was organized with the objective of analyzing the evidence to support newer and some as yet uninvestigated approaches to the use of endocrine therapy in breast cancer. Presentations covered the mechanisms of action of the aromatase inhibitors and the SERMs, as well as the potential for combination or sequential regimens based on the current understanding of the biology of the disease. Breast cancer prevention was another focus of the conference, with updates of ongoing trials and follow-up of trials already analyzed and reported. Fundamentally, the conference participants took stock of what is already known in the endocrine therapy of breast cancer, discussed priorities for future research, and outlined parameters for the design of new trials.

The conference format combined brief scientific reports with extended periods of open discussion. Throughout the formal presentations and discussion periods, the conference chairs asked participants to comment on how the presented data bore upon the following questions, to be addressed in the overview consensus statement:

- What are the basic mechanisms of action and resistance in endocrine therapy of breast cancer?
- What is the role of approved and investigational therapies, both in the adjuvant setting and for treatment of advanced disease?
- How will the new agents be integrated into clinical practice?
- What are the prospects for integrating endocrine therapy with agents inhibiting other pathways involved in tumor cell growth?
- What is the role, if any, for combined or sequential regimens in managing various stages of the disease?
- What clinical data are “missing” and what trials are most needed at this point?

Following the conference, an Executive Committee met in special session to review the conference findings and formulate a summary consensus statement, as follows.

Mechanisms of Action and Resistance in Endocrine Therapy. Understanding of the interaction between nonhormonal pathways and estrogen pathways is steadily advancing. It is becoming clear that the ER is activated by multiple other pathways. Growth factor pathways have been extensively studied, and there are interactions with the PI3 kinase pathway, the mitogen-activated protein kinase pathway, and the stress response pathways (SAPK/JNK and p38 mitogen-activated protein kinase). There are preclinical data demonstrating the potential importance of these interactions, and in fact, clinical trials are already underway to evaluate their significance in patients. Inhibition of growth factor activation using tyrosine kinase inhibitors can delay tamoxifen resistance in in vitro and in vivo models, which provides a rationale for investigating the use of these agents in combination with antineuroestrogens.

The sensitivity of the ER to low levels of circulating estrogen is another potential factor in tamoxifen resistance. When breast cancer cells are deprived of estrogen by long-term endocrine therapy, they tend to become sensitized to respond to progressively lower concentrations of estrogen, which may be a critical component of resistance. A recently discovered mutant ER is reported to be hypersensitive to low concentrations of estradiol, which may then stimulate breast tumor proliferation. The preclinical models now available, as well as the preclinical data already generated, need to be examined for differences among the aromatase inhibitors and the antiestrogens in their...
actions on these multiple pathways that may turn out to be important in early stage disease.

**Endocrine Therapy in Hormonally Responsive Metastatic Disease.** The Executive Committee views nonsteroidal third-generation aromatase inhibitors as first-line therapy for metastatic breast cancer in postmenopausal women, regardless of whether patients have already received tamoxifen as adjuvant therapy. As first-line therapy, aromatase inhibitors have a superior antitumor effect compared with tamoxifen, and patients obtain a more prolonged period of disease control. The aromatase inhibitors are associated with fewer serious side effects, such as thromboembolic complications and endometrial cancer. Moreover, properly selected patients with visceral disease respond well to endocrine therapy.

Aromatase inhibitors are not currently indicated in the treatment of premenopausal women with metastatic disease, as their role in this setting has not been studied. There are a number of hormonal modalities available for premenopausal women, including ovarian ablation, ovarian suppression with LHRH analogues, and tamoxifen. Recent data from a randomized study suggest that there is an advantage for the combination of tamoxifen and ovarian ablation or suppression, compared with tamoxifen alone. Studies are needed to determine whether combining aromatase inhibitors with ovarian ablation or suppression by LHRH would be advantageous for ER+ premenopausal patients.

At this time, the proper sequencing of the available endocrine agents still needs to be defined. There is a pressing need for randomized trials examining the roles of tamoxifen, other antiestrogens, and the steroidal aromatase inhibitors subsequent to therapy with a nonsteroidal aromatase inhibitor. Physicians should recognize that there is a partial lack of class resistance between steroidal and nonsteroidal aromatase inhibitors; therefore, it is appropriate to offer patients steroidal aromatase inhibitors after they have failed nonsteroidal aromatase inhibitors.

By the currently available data from Phase III trials, nonsteroidal SERMs show very little activity in tamoxifen-resistant tumors and are not superior to tamoxifen in first-line therapy. LY353381, a new SERM in Phase II studies, has minimal antitumor activity in tamoxifen-resistant patients. In patients with no prior tamoxifen exposure, this drug has significant antitumor activity. In an ongoing Phase III study its antitumor activity is being compared with tamoxifen. Raloxifene has little antitumor activity and should not be considered as a treatment of existing breast cancer at any stage. Its role in the prevention of breast cancer is being appropriately studied at this time.

Endocrine therapy (with rare exceptions) should not be given to the patient who has been adequately evaluated and found to be both ER- and progesterone receptor-negative by a laboratory with a validated assay.

**Endocrine Therapy in the Adjuvant Setting.** The ER is the most reliable predictive molecular marker. ER status should be determined in all patients, and adjuvant endocrine therapy should be considered for all patients with positive results. If there is any question regarding the reliability of the assay results, they should be repeated. ER-unknown patients should also be considered for endocrine therapy, but every attempt should be made to determine ER status. The small subset of ER−, PR+ patients should also be considered for endocrine therapy. Standardization of ER and progesterone receptor immunohistochemistry is urgently needed for both clinical and research use.

Tamoxifen has been shown in numerous studies and in the Oxford Overview to reduce the risk of recurrence and improve survival when given for 5 years, regardless of patient age and nodal status. The benefit of tamoxifen is the same with or without chemotherapy; in the presence of chemotherapy, the addition of tamoxifen therapy further reduces the risk of recurrence and death.

Ovarian suppression, often combined with tamoxifen, is a reasonable alternative to chemotherapy in selected women. The value of ovarian suppression has not been established clearly when given in conjunction with chemotherapy or when given to women who are still menstruating post-chemotherapy.

The role of aromatase inhibitors in the adjuvant setting is being evaluated in ongoing trials, and some of the results will be forthcoming in the near future. Third-generation aromatase inhibitors are currently being tested alone, against, in sequence with, and in combination with tamoxifen. Common toxicities, serious long-term toxicities, effects on peripheral organs, and contralateral breast cancer risk will all be of importance in evaluating their potential in this setting.

For women in whom tamoxifen is contraindicated or who experience a serious adverse event on tamoxifen, estrogen deprivation with a gonadotropin-releasing hormone agonist is a reasonable alternative for premenopausal women. Under these circumstances, postmenopausal women may be treated with an aromatase inhibitor.

There is no indication for using raloxifene after completion of adjuvant tamoxifen therapy. In tamoxifen-resistant MCF-7 tumors in preclinical models, tumor growth is accelerated with exposure to raloxifene, just as it is with tamoxifen.

**Endocrine Therapy in the Neoadjuvant Setting.** Postmenopausal women with hormone receptor-positive breast cancer will respond to preoperative treatment with aromatase inhibitors or tamoxifen. Prospective clinical trials have shown that neoadjuvant hormonal therapy has a high level of efficacy, and when patients are properly monitored, a low risk for progression. The relative efficacy of endocrine therapy compared with chemotherapy has not been studied, and the integration of these observations into clinical practice is currently not established. Nonetheless, aromatase inhibitors have substantial antitumor activity in endocrine-responsive disease and should be considered in appropriate candidates for neoadjuvant therapy. These might include elderly ER-positive women who would have difficulty tolerating chemotherapy, as well as patients interested in breast-conserving surgery in whom chemotherapy is contraindicated. Women with inoperable local disease or requiring mastectomy are also potentially good candidates for initial treatment with aromatase inhibitor. Neoadjuvant endocrine therapy may have potential as an approach to triaging patients by response to treatment.

The neoadjuvant setting offers important opportunities for more timely research. Studies in metastatic disease may fail to show potential benefits of an investigational therapy because of the many biological defects present in advanced disease. Thus, the perioperative or neoadjuvant setting may serve as an early disease model that is a surrogate for the adjuvant setting. There
is also great potential for biological studies that may yield a better understanding of the mechanisms of breast cancer and the molecular and cellular effects of endocrine therapies. Using pathological end points, neoadjuvant trials offer the possibility of evaluating treatments on a time frame of months rather than decades.

Endocrine Agents for Prevention of Breast Cancer. For all premenopausal women whose risk is $\geq 1.67$ with the Gail model, there is a net benefit in using tamoxifen for risk reduction. This would include women with atypical lobular or ductal hyperplasia and women with lobular carcinoma in situ. For women 50 years and older, the risk/benefit ratio shifts so that higher levels of risk are needed to justify preventive treatment. If the risk is sufficiently high, there is a net benefit even to postmenopausal women. Because the risk/benefit ratio is uncertain in many postmenopausal women, postmenopausal women who are at increased risk are encouraged to participate in the STAR trial, a multiinstitution evaluation of the safety and efficacy of raloxifene against tamoxifen.

The incidence of contralateral breast cancer has been a secondary end point in ongoing adjuvant trials of the aromatase inhibitors. If the results are good and the safety profile is favorable, then these drugs may be the next generation of agents to be studied in a preventive setting.

Potential for Combination Endocrine Therapies. The rationale for investigating combination endocrine therapies is the possibility of modulating downstream targets of multiple pathways implicated in breast cancer progression. It may be possible to prevent or even reverse tamoxifen resistance with newer agents, such as the third-generation aromatase inhibitors, tyrosine kinase inhibitors, and antiestrogens. Moreover, drugs with modest activity as monotherapy may have greater benefit used in combination with agents acting on different pathways for substantially enhanced antitumor effects. The Executive Committee endorses the design of randomized studies to address these questions. Regimens worthy of investigation include: combinations of endocrine agents, given together or sequentially; alternating or dose-escalating approaches; and combinations of endocrine agents and nonendocrine agents that target other pathways implicated in tumor growth and acquired resistance.

Priorities for Future Research. There have been ethical and logistic issues in obtaining blocks in tumor specimens that need to be addressed. There is now a specific, well-developed consent procedure to ask the patient to authorize use of tissue and medical records for unspecified future research. This consent process can and should be incorporated into the initial consultation.

There is a need to explore stepwise, incremental strategies in clinical studies that explore the numerous options of sequential and combination endocrine treatment. Combining SERMs with different agonist/antagonist ratios with aromatase inhibitors is a largely unexplored strategy that deserves study, because the agonist effects of SERMs may be quite different under estrogen-depleted circumstances than as monotherapy.

Work needs to be done to design a drug development program that is based on biological principles. Potential combination and sequential therapies can be explored in preclinical models prior to formal clinical trials. They would then be tested in patients with metastatic disease to provide essential data on safety, pharmacokinetics, and efficacy. However, efficacy data in this setting are not definitive, given that the biology of metastatic disease can be dissimilar to that of earlier-stage disease. Efficacy should be further investigated with pilot studies in the preoperative setting, followed by a formal full-scale neoadjuvant trial if the preliminary safety and efficacy data justify such a study.

Future Conferences. To aid in keeping current of this rapidly evolving field, a yearly multidisciplinary conference on the model of this First International Conference on Recent Advances and Future Directions in Endocrine Manipulation of Breast Cancer can offer direction to the field by reviewing the evidence and the issues concerning endocrine therapy and by formulating new questions for investigation. Signaling mechanisms and pathways are anticipated to be a major topic of the second conference.
Clinical Cancer Research

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