

Second International Conference on Recent Advances and Future Directions in Endocrine Manipulation of Breast Cancer: Summary Consensus Statement¹

Steven E. Come,² Aman U. Buzdar, Carlos L. Arteaga, Angela M. Brodie, Nancy E. Davidson, Mitch Dowsett, James N. Ingle, Stephen R. D. Johnston, Adrian V. Lee, C. Kent Osborne, Kathleen I. Pritchard, Victor G. Vogel, Eric P. Winer, and Carol S. Hart

Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215 [S. E. C.]; University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030-4009 [A. U. B.]; Departments of Medicine and Cancer Biology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-5536 [C. L. A.]; University of Maryland Medical School, Department of Pharmacology, Baltimore, Maryland 21202-1559 [A. M. B.]; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland 21231-1000 [N. E. D.]; Royal Marsden Hospital, Academic Department of Biochemistry, London SW3 6JJ, United Kingdom [M. D.]; Mayo Clinic, Medical Oncology, Rochester, Minnesota 55905-0001 [J. N. I.]; Royal Marsden Hospital and Institute of Cancer Research, Department of Medicine, London SW3 6JJ, United Kingdom [S. R. D. J.]; Baylor College of Medicine, Baylor Breast Center, Houston, Texas 77030-3498 [A. V. L., C. K. O.]; Toronto-Sunnybrook Regional Cancer Centre, Clinical Trials and Epidemiology, Toronto, Ontario, M4N 3M5 Canada [K. I. P.]; Magee-Women's Hospital, UPCI Breast Program, Pittsburgh, Pennsylvania 15213-3180 [V. G. V.]; Dana-Farber Cancer Institute, Boston, Massachusetts 02115 [E. P. W.]; and InforMEDical, Narberth, Pennsylvania 19072-2229 [C. S. H.]

Introduction

The Second International Conference on Recent Advances and Future Directions in Endocrine Manipulation of Breast Cancer, co-chaired by Drs. Aman Buzdar and Steven Come, was held in Cambridge, Massachusetts, June 28-29, 2002.

The conference was organized with the objective of analyzing new preclinical and clinical evidence relating to endocrine therapy of breast cancer. 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, and medical oncology.

Presentations covered ER³ function, models to predict the optimal use of aromatase inhibitors, mechanisms of resistance to

both SERMs and aromatase inhibitors, and the current understanding of cross-talk between estrogen and growth factor signaling pathways. New information regarding the importance of receptor coregulators was emphasized. The potential for combined therapies such as antiestrogens plus growth factor antagonists and sequence issues in the use of endocrine agents were addressed. The importance of models both to explore biological questions and to aid in the selection of the most fruitful approaches for subsequent clinical trials was stressed. Updates of ongoing trials and continued follow-up of reported trials in the advanced disease, adjuvant, and prevention settings were reviewed. 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 considerations for the design of new trials.

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

- What are the basic mechanisms of action and resistance in endocrine therapy of breast cancer?
- What are the roles of approved and investigational therapies, both in the adjuvant and advanced disease settings?
- Should available new data presented change clinical practice? How will the new agents be integrated into clinical practice?
- What is the role for combined or sequential regimens in managing different stages of the disease?
- What are the prospects for integrating endocrine therapy with agents inhibiting other pathways involved in tumor cell growth?
- What data and what trials are most needed, and how can preclinical and presurgical models facilitate progress?

After the conference, an executive committee met in special session to review the conference findings and to formulate a summary statement, as follows.

Mechanisms of Action and Resistance in Endocrine Therapy

Breast cancer growth results from complex interactions between the ER and other signaling pathways. ER-positive breast cancer should not be considered simply a hormonally regulated disease but rather one possessing many complex interrelated mechanisms for growth and survival. Recognition of that complexity will aid in the development of treatment strategies that would target multiple components of the signaling system, for example, ER coactivators as well as the classical ligand/receptor target. There is a growing appreciation of the importance of nonclassical mechanisms of action in which the

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² To whom correspondence should be addressed, at Beth Israel Deaconess Medical Center, Hematology/Oncology Unit, 330 Brookline Avenue, Boston, MA 02215. Phone: (617) 667-4599; Fax: (617) 667-9919; E-mail: scome@caregroup.harvard.edu.

³ The abbreviations used are: ER, estrogen receptor; SERM, selective estrogen receptor modulator.

receptor may bind to other transcription factors rather than to DNA or in which there is direct interaction between ER and plasma membrane-based growth factor receptors. Similarly, growth factor pathways mediate ER function; up-regulation of receptor coactivators is one such mechanism.

The hypothesis that acquired resistance to endocrine therapy is due to the loss of ER (although this undoubtedly occurs in some patients) has been superceded by the accumulated evidence that high levels of coactivators may stimulate growth in the absence of estrogen. In this environment, tamoxifen may exert agonist rather than antagonist effects. Both *in vitro* and clinical data support the hypothesis that coactivators alter the agonist/antagonist balance of SERMs. Furthermore, it has been shown in the laboratory that breast cancer cells grown in estrogen-depleted medium become sensitized to lower concentrations of estrogen, which may also be a form of resistance.

The immediate clinical relevance of these biological studies is twofold. First, none of the endocrine therapies work in the absence of steroid receptors. Endocrine therapy should not be given to the patient who has been adequately evaluated and found to be both estrogen and progesterone receptor negative by a laboratory with a validated assay. Second, continued tamoxifen therapy in the presence of resistance may in fact stimulate tumor growth.

Endocrine Therapy in Hormonally Responsive Metastatic Disease

All three currently available third-generation aromatase inhibitors have firmly established their efficacy as second-line therapy, and the two nonsteroidal aromatase inhibitors, anastrozole and letrozole, are considered to be 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 provide an antitumor effect superior to tamoxifen and a prolonged period of disease control. Importantly, these aromatase inhibitors are associated with fewer serious side effects, such as thromboembolic complications and endometrial cancer. Properly selected patients with visceral disease may respond well to aromatase inhibitor therapy.

At this time, the optimal sequencing of the available endocrine agents still needs to be defined. There is a need for large, randomized trials examining the roles of tamoxifen, the ER down-regulator fulvestrant, and the steroidal aromatase inhibitor exemestane subsequent to therapy with a nonsteroidal aromatase inhibitor. There is a partial lack of cross-resistance between steroidal and nonsteroidal aromatase inhibitors, and it is appropriate to offer patients steroidal aromatase inhibitors after they have failed nonsteroidal aromatase inhibitors.

There are a number of hormonal modalities available for premenopausal women, including ovarian ablation, ovarian suppression with luteinizing hormone-releasing hormone analogues, and tamoxifen. Recent data from a Phase III study as well as a meta-analysis involving patients with metastatic disease support a survival advantage to the combination of tamoxifen and ovarian suppression *versus* tamoxifen alone.

There are no data on the efficacy of the third-generation aromatase inhibitors in premenopausal women; however, the

first-generation agent aminoglutethimide was not effective. There are also no efficacy and limited safety data for fulvestrant in premenopausal patients. The potential roles for these agents need to be defined. In particular, studies are needed to compare alternative regimens of tamoxifen or aromatase inhibitor combined with ovarian ablation or luteinizing hormone-releasing hormone analogue in premenopausal patients. The biology and behavior of the tumor in a premenopausal patient who has been rendered postmenopausal by ovarian suppression are currently unknown. There may be a role for aromatase inhibitors in these patients, but this requires careful investigation of both safety and efficacy issues.

Endocrine Therapy in the Adjuvant Setting

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 be considered for endocrine therapy, but every attempt should be made to determine ER status. The small subset of ER-negative, progesterone receptor-positive patients should also be considered for endocrine therapy.

Tamoxifen has been shown in numerous studies and in the Oxford Overview to reduce the risk of recurrence and to improve survival when given for 5 years, regardless of patient age and nodal status. The benefit of tamoxifen appears to be similar in the presence and absence of chemotherapy, but the database on this issue is limited. When tamoxifen is used in addition to chemotherapy, these treatments should not be administered concurrently but rather sequentially, with tamoxifen initiated after the completion of adjuvant chemotherapy.

In postmenopausal women, third-generation aromatase inhibitors are currently being tested against, in sequence with, and in combination with tamoxifen. The Food and Drug Administration has recently approved anastrozole for treatment of early breast cancer in postmenopausal women with ER-positive disease. Based on the first report of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trial, the aromatase inhibitors appear to be a promising therapy for adjuvant use. These data demonstrate that anastrozole is better than tamoxifen in reducing the risk of recurrence over the short follow-up period reported. Survival data should be available in 2004. Additional data on cognitive, urogenital, and other peripheral organ effects will also be important in evaluating the place of the aromatase inhibitors as adjuvant therapy. Although the results of this large trial are promising, they currently do not change the standard of care, which has been tamoxifen for the past two decades. Whereas there are now data concerning the minor pharmacological differences of the three third-generation aromatase inhibitors, the clinical implications of this information are as yet unknown.

Ovarian suppression combined with tamoxifen is a reasonable alternative to chemotherapy in selected premenopausal women. The value of ovarian suppression has not been established when given in conjunction with chemotherapy or when given to women who are still menstruating postchemotherapy. Tamoxifen and ovarian suppression are suspected to be superior

to tamoxifen alone as in the metastatic setting, but this remains to be established in a clinical trial.

It is recommended that raloxifene not be used after completion of adjuvant tamoxifen therapy. In tamoxifen-resistant MCF-7 tumors in preclinical models, tumor growth is accelerated with exposure to raloxifene, as is the case with tamoxifen.

Neoadjuvant Endocrine Therapy and Preoperative Studies

Postmenopausal women with hormone receptor-positive operable breast cancer will have a good chance to respond to neoadjuvant treatment with an aromatase inhibitor or tamoxifen. Prospective clinical trials have shown that neoadjuvant hormonal therapy has a high level of efficacy and, when patients are properly monitored, low risk for progression. The relative efficacy of neoadjuvant endocrine therapy compared with chemotherapy has not been studied. There is also a need for a randomized study of neoadjuvant *versus* adjuvant endocrine therapy to establish their relative clinical effectiveness and to validate the predictive value of preoperative pathological and biological findings. If reliable surrogate end point biomarkers can be established, neoadjuvant trials offer the possibility of evaluating treatments on a time frame of months rather than years, facilitating the movement of useful strategies into clinical practice.

The preoperative setting offers important opportunities for research. Previously treated advanced breast cancer may not accurately reflect the biology of early, untreated disease. Studies in metastatic breast cancer may fail to show potential benefits of an investigational therapy because of these differences. Preoperative biological trials also provide a unique opportunity to study the molecular and cellular effects of endocrine therapies, possible mechanisms of endocrine resistance, and the potential interactions of these drugs with other agents. In a 2-week interval between diagnostic biopsy and definitive surgery, the biological effects of agents with established safety and activity can be studied. Therapies of proven value can also be evaluated in combination with investigational agents whose safety has been otherwise determined. Because these short-term “incidental” studies do not promise benefit to individual patients, issues of safety, ethical consenting, and accrual are important considerations.

Endocrine Agents for Prevention of Breast Cancer

The Breast Cancer Prevention Trial P-1 showed that tamoxifen offers a net benefit for premenopausal women whose 5-year risk is 1.67% or greater with the Gail model, a conclusion that is further supported by the recent meta-analysis by the American Society of Clinical Oncology (ASCO) Cancer Technology Assessment Working Group. This would include women with atypical lobular or ductal hyperplasia and women with lobular carcinoma *in situ*. This trial has now completed 5 years of follow-up in all subjects and will report final data later this year.

For women 50 years and older with an intact uterus, 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. Postmenopausal women who are at increased risk are encouraged to participate

in the STAR trial, a multi-institution evaluation of the safety and the efficacy of raloxifene against tamoxifen. The STAR trial has completed 60% of its target accrual within its first 3 years.

These large trials were undertaken based on mature data from adjuvant therapy trials. For new compounds such as the signal transduction inhibitors, such adjuvant data will not be available for many years. There is a clear need for prevention therapy models that would move promising compounds more rapidly to clinical trials.

Cross-Talk and Combination Endocrine Therapies

Great progress has been made in the understanding of signal transduction by polypeptide growth factor receptor tyrosine kinases. Whereas the complexities of signaling pathways and their cross-talk are increasingly apparent, intermediates common to multiple pathways have been identified. These common intermediates will both allow further understanding of the interactions between pathways and provide potential therapeutic targets. Combinations of endocrine therapies and receptor tyrosine kinase inhibitors afford the possibility of simultaneously modulating multiple mechanisms implicated in breast cancer progression. Preclinical data have already demonstrated that epidermal growth factor receptor tyrosine kinase inhibitors have the potential to delay or even reverse resistance to tamoxifen. Preclinical studies have also demonstrated that overexpression of HER2/neu may cause resistance to antiestrogens through both mitogen-activated protein kinase and Akt pathways. Furthermore, newly presented clinical data suggest that overexpression of HER2/neu may mediate tamoxifen resistance through activation of the ER coactivator AIB1. Clinical trials combining endocrine therapies and signal transduction inhibitors are a high priority.

In studying the new paradigm presented by cross-talk, it is possible that drugs with modest or no activity as monotherapy could have substantial benefit when combined with agents acting on different pathways or elsewhere on the same pathway. Preclinical models and preoperative therapeutic and “incidental” studies offer the potential for identifying strategies that should progress to large clinical trials.

Priorities for Future Research

Further progress in understanding the biological basis of breast cancer response and resistance to endocrine therapy can be facilitated by a change in the research paradigm. Whereas past efforts have focused largely on clinical outcomes, a growing ability to measure alterations in intracellular pathways before and after a treatment affords an opportunity to develop rational strategies for endocrine and biological therapies. To facilitate these efforts, the logistics of obtaining tissue for study must be improved. Consent to allow the use of tissue blocks for both present and future research should be incorporated into the consent forms, and the availability of blocks should be a requirement in future trials, with fresh tissue acquisition a high priority. Most present and past clinicopathological correlations link tumor characteristics on an initial diagnostic biopsy to treatment outcomes that are often many years and therapies later. Repeat biopsies just before, during, and after therapy should be incorporated into research studies wherever feasible,

thus allowing determination of the effects of the specific intervention on tumor biomarkers. Newly developed phospho-specific antibodies to ER α and activated signal transducers of tyrosine kinase networks as well as gene array technologies and mass spectrometry approaches are likely to be productive of valuable information.

The use of presurgical clinical studies, both therapeutic and incidental, should be expanded. These studies are particularly valuable for two reasons. First, tissue is available at both ends of the intervention. Second, the biological profile of untreated malignancy is likely to differ from that of pretreated disease. Therapies discarded as ineffective in advanced disease could prove useful in early disease or in the prevention setting. Furthermore, if biological and pathological end points measured in presurgical studies can be validated as predictive of outcome, the clinical trials process could be significantly accelerated.

Preclinical models continue to make important contributions to endocrine therapy of breast cancer. Human cell lines in xenografts have afforded an understanding of the mechanisms

of action and resistance with endocrine therapies and are proving useful in assessing cross-talk between signaling pathways. Although surprisingly few, these models have been highly predictive of human treatment results with SERMs and aromatase inhibitors. Results obtained in these models should be useful in design of trials. As the emphasis of endocrine therapies moves to the area of prevention, it should be noted that there is a scarcity of validated animal systems that would model early phases of the disease in which preventive approaches can be tested and explored.

Ironically, our rapidly advancing knowledge of tumor biology and the multitude of available, potentially therapeutic compounds that could be used singly, in combination, and in sequence pose a problem: there are so many avenues that could be explored in clinical trials. The development of treatment strategies should proceed in an orderly sequence based on biological principles. Preclinical models may be used to identify the most promising approaches that can then be piloted in presurgical studies before large-scale clinical studies are undertaken.