# Current Understanding of Endocrine Therapy for Breast Cancer

Department of Surgery, Kangnam St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

**Woo-Chan Park, M.D., Ph.D.**

In the treatment of breast cancer, especially in estrogen receptor (ER) positive patients, endocrine therapy has played an important role since bilateral oophorectomy, the first endocrine therapy, was performed by George Thomas Beaston in 1896. Thereafter, various therapeutic modalities such as radiation therapy to ovaries, surgical or medical adrenalectomy, or hypophysectomy, have been used for endocrine therapy in breast cancer. The discovery of ER and the development of anti-estrogens represent substantial progress, and tamoxifen, the first selective ER modulator, has become the gold standard in the endocrine therapy of breast cancer. The therapeutic effects of tamoxifen were confirmed by the 1995 Oxford overview. Recently, the 7th International Conference on Adjuvant Therapy of Primary Breast Cancer held in St. Gallen, Switzerland, recognized the increasing role played by endocrine therapy in properly selected patients groups, especially in younger patients with ER-positive tumors. In addition, recent advances in estrogen research and ER function at the molecular level have provided new strategies as well as a better understanding of endocrine therapy for breast cancer. Lately, new hormonal agents, such as the third-generation aromatase inhibitors, and ER downregulators, showed equivalent or better results in terms of therapeutic effects than tamoxifen. As a result, many clinical trials are ongoing to determine the most appropriate endocrine therapy for breast cancer. Therefore, it is important to maximize the benefits of endocrine therapy in clinical practice in terms of the patient's quality of life as well as the prolongation of patient survival. More studies are needed to determine optimal agents and the duration of therapy, combinations of agents or sequences of therapy according to prognostic and predictive factors. **(Journal of Korean Breast Cancer Society 2002;5:212-216)**

**Key Words:** Breast cancer, Endocrine therapy, Review

Correspondence: Woo-Chan Park, Departmnet of Surgery, Kangnam St. Mary's Hospital, The Catholic University of Korea, #505 Banpo-dong, Seocho-gu, Seoul 137-701, Korea. (Tel) 82-2-590-2728, (Fax) 82-2-590-1406, (E-mail) wcpark@catholic.ac.kr

## INTRODUCTION

Historically the endocrine therapy of breast cancer originated from a novel concept proposed by George Thomas Beaston, a surgeon in Glasgow. In 1896, he published a paper about the successful treatment of a premenopausal woman with recurrent breast cancer by bilateral oophorectomy. Actually, the principal hormone of the ovary, estrogen, was identified in 1923. Thereafter, many efforts were made to prevent estrogen production by means of radiation to ovaries, bilateral adrenalectomy, or hypophysectomy. Endocrine therapy experienced a step change in the 1960's when the estrogen receptor (ER) was discovered. This led to the elucidation of the mechanisms of estrogen action and established ER as a new target of endocrine therapy. Tamoxifen, the first selective ER modulator (SERM), has been the gold standard in the endocrine therapy of breast cancer since the drug had first been approved in the 1970s for the treatment of advanced breast cancer in the UK and the USA. Over the last 8 years, tamoxifen has been considered to be the main means of reducing mortality from breast cancer in western countries.(*1*)

The impact of endocrine therapy for breast cancer was confirmed by the 1995 Oxford overview.(*2*) Recently, new endocrine agents with various action mechanisms, such as the third-generation of aromatase inhibitors, and ER downregulators, revealed equivalent or better results in the treatment of breast cancer as tamoxifen. The 7th International Conference on Adjuvant Therapy of Primary Breast Cancer held at St. Gallen, Switzerland, also recognized the increased role of endocrine therapy in properly selected patients groups, especially in younger patients with ER-positive tumors.(*3*) At present, numerous trials are ongoing to determine optimal endocrine therapy for breast cancer. In addition, recent advances in research upon estrogen and ER function at the molecular level have provided new strategies and a better understanding of endocrine therapy for breast cancer. Accordingly, in this review, we have attempted to summarize the basic concepts of

estrogen and ER function and recent clinical data upon endocrine therapy for breast cancer in an effort to promote optimal decision-making in cases of breast cancer.

## BASIC CONCEPTS OF ENDOCRINE THERAPY FOR BREAST CANCER

### 1) Estrogens and ablation therapy

Estrogens are known to be related to the development and progression of breast cancer as well as to the normal development of the breasts. The naturally occurring estrogens are estradiol and estrone. The most important, as well as the most potent, estrogen secreted by the ovary is estradiol-17β. Estrone is principally sourced from the extraglandular conversion of androstenedione in adipose tissue. In postmenopausal or castrated women, the major source of estrogen changes from ovarian secretion to the peripheral conversion of androstenedione secreted by the adrenal gland, to estrone by aromatase. Therefore, it is a rational strategy to remove the sources of estrogens in breast cancer; i.e. ovarian ablation by surgery or radiation, or ovarian suppression by LHRH agonists in premenopausal patients, and surgical or medical adrenalectomy in postmenopausal patients, the later of which is now replaced by the third-generation aromatase inhibitors.

### 2) Estrogen receptors and ER targeted therapy

Estrogens exert their function by binding to estrogen receptors (ERs). So far, two ERs are identified, ERα and ERβ, but the function and role of ERβ have not been clearly defined. On the other hand, the action mechanisms of ERα have been studied in detail at the subcellular level, and clinically ERβ works as one of the most powerful prognostic and predictive factors for the treatment of breast cancer.

The binding of ERs with estrogen starts a series of events; the dissociation of heat shock proteins, receptor dimerization, the initiation of activation function 1 and 2 (AF-1 and AF-2), nuclear localization of the ER and binding to estrogen response elements (ERE), recruitment of activation cofactors, and transcription and tumor cell proliferation.(*4*)

Selective ER modulators (SERMs), such as tamoxifen or raloxifene, bind with ERs and initiate a similar series of events, but only AF-1 is active and able to recruit activation cofactors, and partially activate transcription with a reduced rate of tumor cell proliferation. They function as agonists or antagonists as modulated by coregulators of ER transcription.(*5*) The dual actions of SERMs explain why the serious side effects of tamoxifen, which include endometrial cancer or thromboembolic problems occur and why raloxifene is approved for the prevention of osteoporosis and breast cancer, but not for the treatment of breast cancer.

Fulvestrant (Faslodex, formerly ICI 182,780) is a potent steroidal anti-estrogen that mediates its effects by estrogen receptor downregulation.(*6*) It appears to act as a pure anti-estrogen and exhibits none of the negative side effects of tamoxifen. It has been shown to be as effective as aromatase inhibitors in postmenopausal women with advanced breast cancer who have progressed on endocrine therapy, principally tamoxifen.(*7*) Therefore, Fulvestrant provides the clinician with an alternative therapeutic strategy in cases showing the development of tamoxifen resistance.

The mutations of ER play roles in the development of tamoxifen resistance or of hypersensitivity to estrogen. D351Y ERα mutation was found in a tamoxifen-stimulated breast cancer derived from MCF-7 breast cancer cells.(*8*) In MDA-MB-231 breast cancer cells stably transfected with wild-type ERα or D351Y mutant ER, raloxifene showed antagonistic actions with wild-type ERα, but agonistic actions with mutant ERα.(9) A series of structure-function studies of D351Y mutant ERα and different side-chains on SERMs show a predictable modulation of the SERM-ERα complex.(*10-12*) Another important mutation, K303R ERα, was detected in premalignant breast lesions by microdissection.(*13*) Cells containing this mutation showed hypersensitivity to estrogen and the mutation was found much more frequently in patients with more-advanced, node-positive breast cancer.(*14*) Therefore, it is hypothesized that the K303R ERα mutation could play an important role in the progression of breast cancer, and it is sure that Er is a major target in the endocrine therapy of breast cancer.

### 3) New endocrine therapy

In the absence of estrogen, ER can be activated by phosphorylation through other pathways, such as the PI3K/Akt (PKB) pathway, the MAPK (Erk1/2) pathway, and the stress response pathway.(*15*) In addition, it is well known that cross-talk between ER and growth factor receptor pathways are important in the development of resistance to specific endocrine therapies. Therefore, simultaneous clinical applications of inhibitors of the growth factor pathway, by tratsuzumab or tyrosine kinase inhibitors, combined with endocrine therapy are being investigated.(*16*)

## CLINICAL CONSIDERATIONS OF ENDOCRINE THERAPY FOR BREAST CANCER

### 1) Responsiveness of endocrine therapy

The response of endocrine therapy could be predicted by the steroid hormone receptor status of the primary tumor. According to the benefits expected on the based of clinical data, endocrine therapy should be restricted to ER and/or PR-positive tumors.(*2*) Moreover, it has been recommended that immunohistochemistry be used rather than ligand-binding assays to determine endocrine responsiveness.(*17*) Even though the exact threshold of ER and/or PgR staining is unknown, approximately 10% positive staining of cells for either receptor could be considered a reasonable threshold.(*18*)

### 2) Endocrine therapy in a adjuvant setting

Adjuvant endocrine therapy should be considered for all patients with ER-positive results by the standard ER/PR assay. Tamoxifen has been the gold standard for adjuvant endocrine therapy for breast cancer, regardless of patient age and nodal status. According to the Oxford overview(*2*) and the National Surgical Adjuvant Breast and Bowel Project B14,(*19*) the optimal duration of tamoxifen therapy is 5 years. Two trials are ongoing to resolve the issue of the duration of tamoxifen therapy, the ATLAS trial (Adjuvant Tamoxifen: Longer Against Shorter), and the atom trial (adjuvant Tamoxifen Treatment).

In premenopausal patients, the reduction in the risk of recurrence by ovarian ablation or suppression alone is comparable to that of CMF chemotherapy.(*20*) In addition, the combination of LHRH agonist plus tamoxifen showed no difference in terms of disease-free or overall survival versus CMF chemotherapy.(*21*) The combination of ovarian ablation with chemotherapy was thought to have no benefit in premenopausal patients.(*22*) However, a recent study suggested that endocrine therapy in addition to chemotherapy is of benefit in young patients with ER-positive breast cancer.(*23*)

Currently the third generation of aromatase inhibitors are being evaluated in postmenopausal patients in an adjuvant setting versus tamoxifen, and these may be used when tamoxifen is contraindicated or when toxicity of tamoxifen is evident.(*24*)

### 3) Endocrine therapy in a metastatic setting

In the treatment of postmenopausal patients with ER-positive metastatic disease, non-steroidal third-generation aromatase inhibitors are considered the first-line therapy, regardless of previous adjuvant therapy with tamoxifen.(*25-27*)

For premenopausal patients with ER-positive metastatic disease, the combination of LHRH agonists and tamoxifen showed better results than either agent alone in terms of progression free survival or overall survival,(*28*) and now combination therapy involving ovarian suppression and aromatase inhibitors is being tested.

So far, the proper sequencing of the available endocrine agents has not been determined.

### 4) Endocrine therapy in a neoadjuvant setting

In postmenopausal patients who are interested in breast-conserving surgery, but in whom chemotherapy is contraindicated or who have inoperable disease, neoadjuvant endocrine therapy can be considered, because aromatase inhibitors have a substantial antitumor effect in ER-positive postmenopausal patients.(*29*)

### 5) Endocrine therapy in the prevention of breast cancer

The benefits of using tamoxifen to reduce the incidence of breast cancer in high-risk women, regardless of menopausal status, or to reduce the incidence of contralateral breast cancer were confirmed by the NSABP P-1 study(*30*) and by an adjuvant therapy database.(*2*) However, the risk and benefit ratio of tamoxifen should be considered, especially in postmenopausal women, because this is uncertain in many postmenopausal women. In addition, the MORE (Multiple Outcomes Raloxifene Evaluation) trial reported that raloxifene plays a role in the reduction of the risk of invasive breast cancer in postmenopausal women with osteoporosis.(*31*) Now, a comparative study of tamoxifen and raloxifene (STAR) trial is ongoing to compare their relative merits for the prevention of invasive breast cancer, and their effects on the cardiovascular system, bones, and their general toxicities.(*32*)

## CONCLUSION

In the management of breast caner, patients with an ER-positive tumor definitely benefit from endocrine therapy, in terms of therapeutic or preventive effects as well as its well tolerated toxicity. Recently, the role of endocrine therapy has recognizably increased in younger premenopausal patients with ER-positive tumors. Currently, various endocrine agents are available for the treatment of breast cancer, therefore, it is important to maximize the benefits of endocrine therapy in clinical practice in terms of the patient's quality of life the prolongation of survival. More studies are needed to determine the optimal

agents and the duration of therapy, combinations of agents or the sequence of therapy according to prognostic or predictive factors of patients.

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