Understanding the estrogen receptor signaling pathway: focus on current endocrine agents for breast cancer in postmenopausal women

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Estrogen receptor (ER) signaling plays a critical role in many breast cancers. As a result, endocrine therapy is a mainstay in the treatment plan for patients with hormone receptor-positive breast cancer. Although patients with metastatic breast cancer (MBC) are often given several lines of endocrine therapy throughout the course of their disease, the optimal sequence of and exact mechanisms of resistance to endocrine therapy remain unclear. Endocrine therapies include aromatase inhibitors, selective ER modulators, and selective ER downregulators. These agents interfere with ER signaling and inhibit breast cancer growth, but their mechanisms of action (MOAs) are distinct and potential mechanisms of resistance vary. Patient-specific factors (eg, tumor characteristics, burden of disease, patient preferences, and treatment history) and the MOAs of the available agents are important considerations. This review discusses the latest understanding of ER biology, the mechanistic differences between endocrine therapies, and future directions in endocrine therapy for MBC.

It is well established that estrogen acting via the estrogen receptor (ER) plays a role in the growth and development of hormone receptor-positive (HR+) breast cancer. As a result, over the past few decades, several endocrine therapies that limit the actions of estrogen have been developed. These endocrine therapies have played a substantial part in the treatment of breast cancer and have significantly improved the outcomes of postmenopausal women with all stages of the disease.

Although many different agents have been used in the clinic to treat these patients, aromatase inhibitors (AIs) and antiestrogens form the two major categories of endocrine therapy in current use. These two types of agents have distinct mechanisms of action (MOAs).[1] AIs reduce circulating estrogen levels by preventing the conversion of androstenedione into estrogen in peripheral tissues.[1] Antiestrogens, also referred to as ER antagonists, can be further classified into two subgroups based on their MOA: the selective ER modulators (SERMs), typified by tamoxifen, and the selective ER downregulators (SERDs), exemplified by fulvestrant (Faslodex).[1]

A number of randomized clinical studies have demonstrated the efficacy of tamoxifen and the AIs (anastrozole, letrozole, and exemestane) in the adjuvant[2–5] and metastatic[6–8] settings. Fulvestrant has demonstrated effectiveness in the metastatic setting.[9–13]

Mechanistic overview of endocrine therapies

Estrogen signaling in postmenopausal women

To understand the MOAs of available endocrine therapies, it is first essential to discuss how estrogen production and ER signaling work in postmenopausal women. Prior to menopause, the ovaries produce the majority of circulating estrogen. Following menopause, estrogen production by the ovaries ceases, and the overall concentration of circulating estrogen is decreased. However, smaller amounts of estrogen are produced by various sources outside the ovaries. This residual estrogen production can play a central role in breast cancer growth in postmenopausal women. Estrogen precursors are predominantly synthesized by the adrenal glands. Circulating estrogens (estrone and estradiol) are

then produced by the aromatization of these estrogen precursors or androgens (androstenedione and testosterone) in a number of tissue types, including the skin and subcutaneous adipose tissue.[14] For example, androgens can be converted to estrogen in the adipose fibroblasts associated with breast tumors, stimulating malignant proliferation.[15–17]

ERs are localized in the nucleus and in the cytoplasm near the cell membrane in the presence or absence of estrogen.[18] ERs shuttle back and forth between these locations to transmit signals that stimulate transcription of estrogen-responsive genes. Estrogen exerts its effects through the ER to stimulate cell growth in two major ways: ligand-dependent receptor activation (the classic pathway) and nongenomic (or non-nuclear) actions.[19,20] The proliferative activity mediated by the ER is attributed to two structural domains—an activating function 1 (AF-1) domain and a ligand-inducible activating function 2 (AF-2) domain—which, as discussed below, have independent and synergistic effects, depending on circumstances such as the presence of ligand or various coactivator proteins.[21] In the classic pathway of ER activation, binding of estrogen to the ER causes the receptor to dissociate from an inhibitory complex with chaperone proteins, exposing the AF-2 domain on the ER.[22] This action allows formation of ER homodimers and increased nuclear localization, where these homodimers bind to sequences of DNA known as estrogen response elements (EREs) and promote transcription of key genes. This process is driven by various coactivator proteins recruited by the AF-1 and AF-2 domains. The activation of both AF domains is required for estrogen to exert its full agonist effects.[22] Notably, the AF-1 domain is exposed prior to as well as after estrogen binding. Therefore, the activity of the AF-1 domain is hormone independent and is thought to
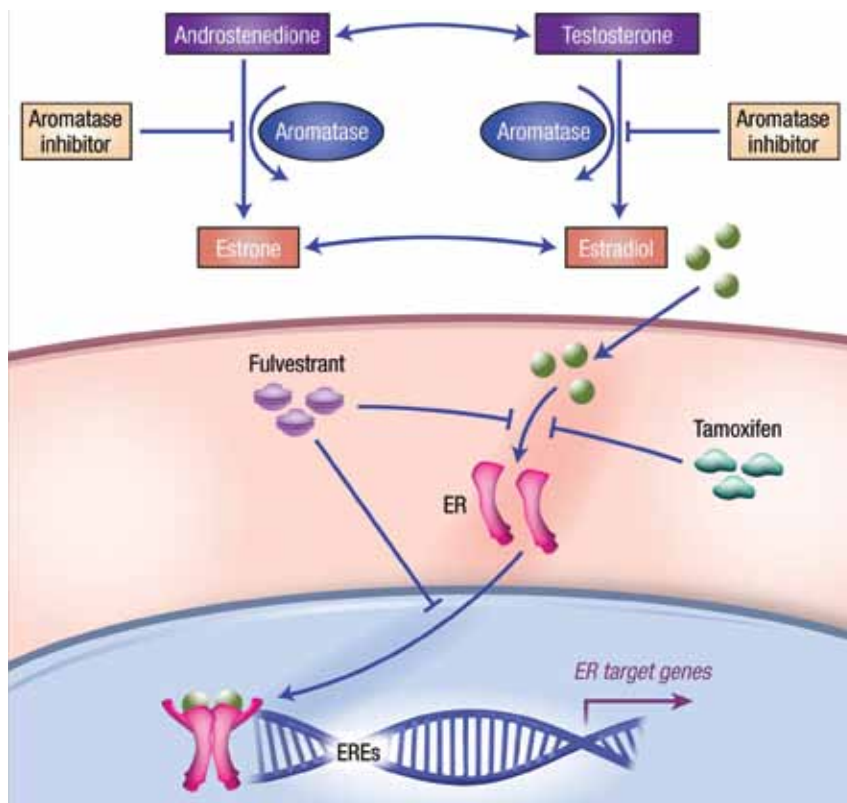
FIGURE 1 The basis for endocrine therapy in breast cancer. ER = estrogen receptor; EREs = estrogen response elements. Reprinted by permission from Macmillan Publishers Ltd: Johnston SR, Dowsett M. Aromatase inhibitors for breast cancer: lessons from the laboratory. Nat Rev Cancer 2003;3:821–831, Copyright 2003.

be regulated by crosstalk with other signaling pathways during ligand-independent activation of ERs.[23]

In nongenomic activation, estrogen binds ERs in the cytoplasm. The activated ERs crosstalk with and activate various intracellular signal transduction pathways, such as those mediated by mitogen-activated protein kinases (MAPKs), AKT, and phosphatidylinositol 3-kinase (PI3K) to initiate gene transcription.[19,24]

MOAs of AIs

Starting with the first-generation AI, aminoglutethimide, several AIs have been developed over the past few decades.[25] Fine-tuning the selectivity for aromatase has improved the safety and efficacy of these agents. The third-generation AIs (including the reversible nonsteroidal agents [ie, anastrozole and letrozole]) and the ir-

reversible steroidal agent (ie, exemestane) are currently used in clinical practice.[25,26] Despite their structural differences, the steroidal and nonsteroidal AIs have nearly identical MOAs, except that steroidal AIs bind irreversibly, whereas nonsteroidal AIs bind reversibly. AIs inhibit the conversion of androgens into estrogens by binding to and inhibiting the enzyme aromatase (Figure 1).[14] As a result, despite the subtle differences between agents, more than 95% of aromatase is suppressed and estrogen levels are reduced by about 90%.[25,27–29]

AIs do not inhibit the production of estrogen by the ovaries and thus are not approved to treat breast cancer in premenopausal women. However, there is evidence to suggest potential for combination therapy with the AI anastrozole plus goserelin (Zoladex) in premenopausal women with advanced

breast cancer (ABC). For example, as first-line therapy, the anastrozole-goserelin combination resulted in a 98% reduction (pretreatment to 6 months) in median estradiol levels and produced a sustained clinical benefit.[30] Previous work by the same group has shown similar activity of this combination as second-line therapy.[31]

MOAs of antiestrogens

Antiestrogens, including SERMs and SERDs, work similarly in that they block estrogen from binding to ERs. However, within this class of drugs, the exact MOA for each agent varies in the potential for agonist effects and the effects on ER expression. The differing effects of antiestrogens are described here.

Selective ER modulators. SERMs such as tamoxifen, raloxifene (Evista), and toremifene (Fareston) have unique chemical structures and exhibit a mix of agonistic and antagonistic effects in different tissues (Figure 2).[19,22,32] For example, tamoxifen, which binds to ERs with lower affinity compared with estrogen (about 2.5% that of estrogen), acts as a competitive inhibitor to estrogen for the ER.[33] The binding of tamoxifen to the ER induces a conformational change, which causes the AF-2 domain to become hidden, inhibiting some coactivator recruitment and transcription of genes that depend on AF-2 activation (Figure 3).[23,34] However, the AF-1 domain remains exposed. Tamoxifen binding also induces ER dimerization and DNA binding and stimulates AF-1–mediated gene transcription.[23,34] A combination of AF-1 activation and tissue-specific expression of ER coactivator and corepressor molecules is responsible for the partial agonist properties of tamoxifen.[19]

Preclinical studies of tamoxifen have shown antagonist activity in mammary tissue but partial agonist activity in the uterus as well as agonist activity in bone and cholester-
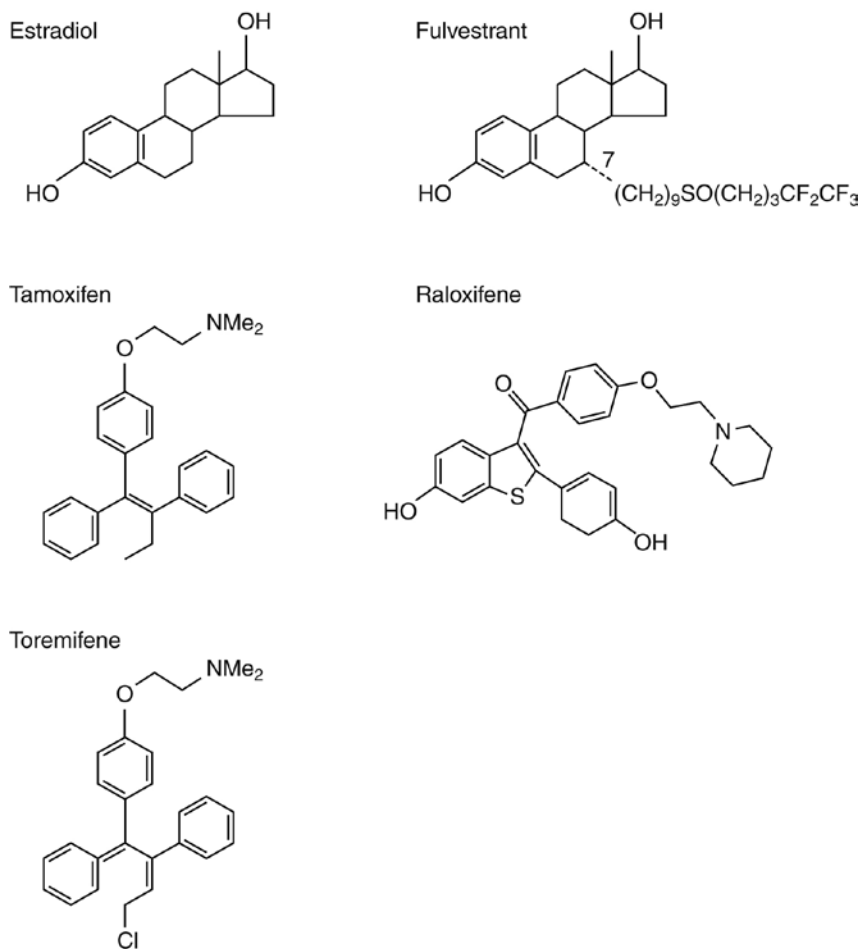
FIGURE 2 Structures of estrogen (estradiol) compared with estrogen receptor antagonists. Source: Howell[22] and Buzdar and Hortobagyi.[32]

ol metabolism.[35] Partial agonist effects of tamoxifen on the uterus were demonstrated in a preclinical study in rats.[36] This study showed that tamoxifen stimulated uterine proliferation (as measured by uterine weight) in a dose-dependent manner; however, the increase in uterine proliferation was less than the proliferation induced by estradiol treatment. The partial agonist activity of tamoxifen is thought to impact its clinical side-effect profile and protective effects on bone.

In contrast, raloxifene acts as an antagonist in both mammary tissue and the uterus as well as an agonist in bone and cholesterol metabolism.[1,37] Although the exact reasons for these differences have not been fully elucidated, it is likely that structural differ-

ences among the SERMs contribute to their variable effects.

Selective ER downregulators. Pure antiestrogens like fulvestrant have no known agonist effects.[35] Fulvestrant binds to the ER with 89% affinity compared with estradiol and prevents estrogen binding.[38] Fulvestrant has a structure similar to that of estrogen, except it contains a heavily fluorinated alkylamide arm at the 7α position, which increases binding affinity for the ER relative to tamoxifen (Figure 2).[22,38]

Fulvestrant binding induces a conformational change in the receptor, which inactivates both the AF-1 and AF-2 domains and prevents ER homodimerization (Figure 3).[34,39–41] Because fulvestrant interferes with
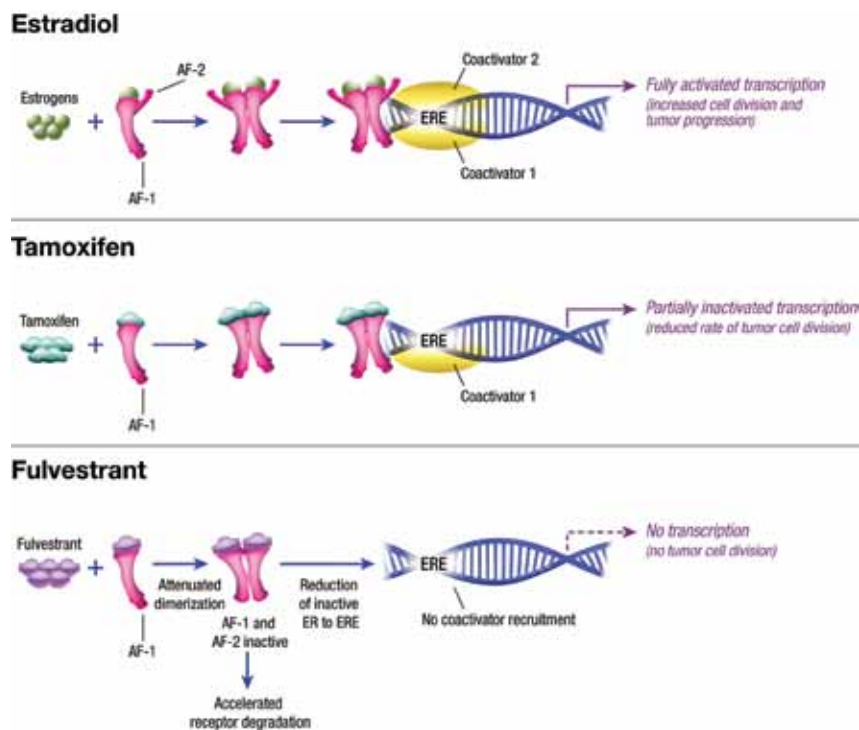
FIGURE 3 Comparison of the actions of estrogen, tamoxifen, and fulvestrant. AF-1 = activating function 1 domain; AF-2 = activating function 2 domain; ERE = estrogen response element; ER = estrogen receptor. Reprinted by permission from Wolters Kluwer Health: Howell A. Is fulvestrant ("Faslodex") just another selective estrogen receptor modulator? Int J Gynecol Cancer 2006;16(suppl 2):521–523, Copyright 2006.

the action of both the AF-1 and AF-2 domains, estrogen-mediated transcriptional activation is fully inhibited, resulting in no agonistic effects.[22,42] The lack of agonist effects of fulvestrant on the uterus was demonstrated in a preclinical study in rats.[38] Unlike tamoxifen, fulvestrant had no effects on uterine proliferation when compared with estradiol treatment, which stimulated uterine proliferation and increased uterine weight.

Fulvestrant treatment also impairs shuttling of ER between the nucleus and the cytoplasm, essentially trapping ER in the cytoplasm.[43] Fulvestrant treatment results in an increased ER turnover and decreased ER half-life, which lead to a reduction in ER levels.[40,42,44,45] Fulvestrant binding induces rapid degradation of ER via the ubiquitin-proteasome pathway.[46–48]

In a neoadjuvant clinical study, fulvestrant treatment significantly reduced ER and progesterone receptor (PgR) levels in a dose-dependent manner, as measured in tissue samples taken before and during surgery (Figure 4).[45] Notably, tissue samples taken from patients treated with tamoxifen showed a reduction in ER levels but an increase in PgR levels. The increase in PgR levels associated with tamoxifen is likely due to its partial agonist activity, as PgR expression is controlled by ER signaling and indicates at least some ER activity.[45]

The phase II NEWEST trial compared high-dose fulvestrant (500 mg/month plus 500 mg on day 14 of month 1) with low-dose fulvestrant (250 mg/month) in the neoadjuvant setting for postmenopausal women with newly diagnosed, ER-positive, local ABC. Data showed that the high-dose fulvestrant regimen resulted in greater reductions in the Ki67 labeling index and superior downregulation of both ER and PgR expression.[49,50]

Although fulvestrant induces rap-

id ER degradation, production of new ERs is not affected. Therefore, the tumor remains ER positive, and the patient remains eligible for subsequent hormonal therapy, if appropriate. Retrospective analyses of data from phase II/III trials of fulvestrant support the fact that patients may retain sensitivity to other hormonal agents after treatment with fulvestrant.[51,52] In one study, of the 54 patients who derived clinical benefit from fulvestrant in a second-line setting and went on to receive subsequent hormonal therapy, 25 had a clinical benefit (4, partial responses; 21, stable disease).[51] In another study, of 28 patients achieving an initial clinical benefit on fulvestrant, subsequent endocrine therapy resulted in 2 partial responders, 11 patients with stable disease, and 15 patients with progressive disease at 6 months.[52]

The MOAs of fulvestrant and tamoxifen are similar; however, a number of distinct actions of each agent support their sequential use. In addition, preclinical and clinical evidence has shown that fulvestrant prevents tumor growth and improves clinical outcomes in tamoxifen-resistant tumors, further supporting the fact that fulvestrant is not cross-resistant with tamoxifen.[11,53]

Two relatively recent studies have also examined the optimal dosage of fulvestrant in postmenopausal patients with HR+ ABC; they have shed light on another important aspect of the use of endocrine therapy, one related to pharmacokinetics and dose-related effects.[12,13] The FIRST trial compared anastrozole (1 mg/day) with fulvestrant (500 mg/month). Investigators demonstrated that fulvestrant was at least as effective as anastrozole in terms of clinical benefit rate and had a longer median time to disease progression.[13]

The CONFIRM trial was a large phase III study that compared 500 mg and 250 mg of fulvestrant in patients with HR+ ABC that had progressed or relapsed following previous
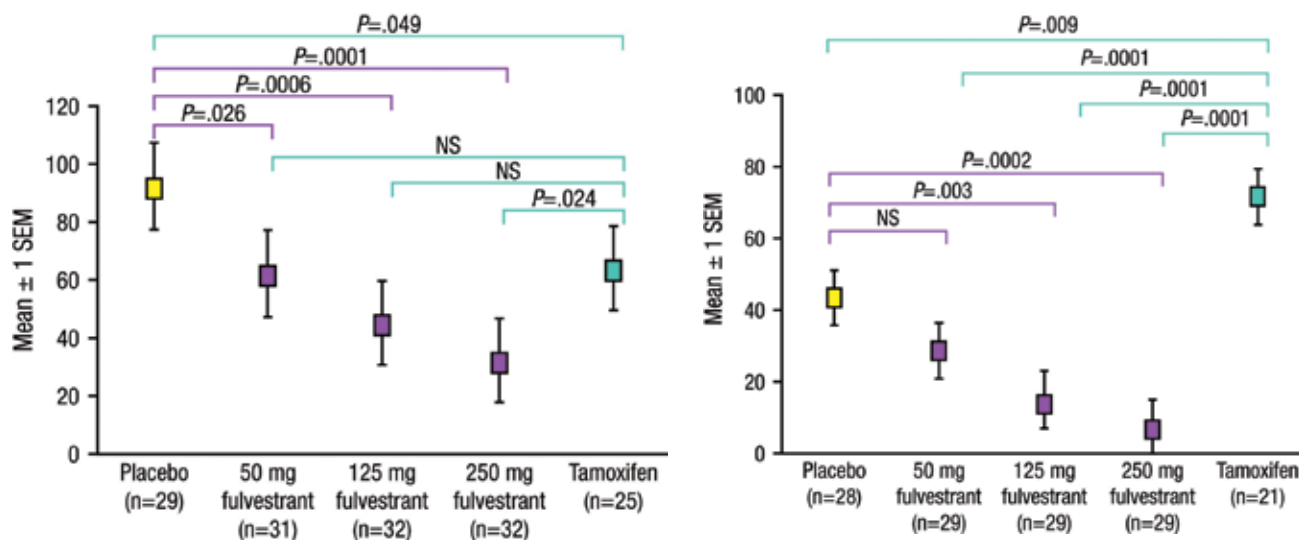
FIGURE 4 Effects of fulvestrant and tamoxifen on estrogen receptor *(left)* and progesterone receptor *(right)* expression. SEM = standard error of the mean; NS = not significant. Cancer research by Robertson JF, et al. Copyright 2001 by American Association for Cancer Research. Reproduced with permission of American Association for Cancer Research in the format Journal via Copyright Clearance Center.

hormonal therapy.[12] Compared with 250 mg, the 500-mg dose significantly improved progression-free survival (PFS; 5.5 months vs 6.5 months, respectively; hazard ratio, 0.80 [95% confidence interval: 0.68, 0.94]; *P* = .006). As a result of these studies, both the US Food and Drug Administration and the European Union have recently granted approval of fulvestrant at the 500-mg/month dose for the treatment of postmenopausal women with HR+ MBC whose disease has recurred or progressed after antiestrogen treatment.

Considerations for endocrine sequencing

Despite the success of these agents in the treatment of breast cancer, up to 40% of women with early breast cancer and most patients with MBC experience disease progression.[54] However, preclinical and clinical data suggest that after the development of resistance to one type of endocrine therapy, ER signaling still plays an important role.[55] Approximately 40%–50% of patients who initially respond to endocrine therapy are likely to respond to subsequent endocrine therapies.[56] Therefore, many of these

patients may benefit from sequential use of endocrine therapy at the time of disease progression.[56,57]

Although a substantial amount of preclinical and clinical data support the use of sequential endocrine therapy in patients with disease progression after initial endocrine therapy, the optimal sequence is only beginning to be determined.[58] For example, the phase III EFECT study showed that exemestane and fulvestrant were similar in terms of time to disease progression, overall response rate, and clinical benefit rate in postmenopausal women with hormone-positive ABC who received prior treatment for breast cancer with a nonsteroidal AI.[59]

In addition, current guidelines do not specify which MBC treatment would be optimal after resistance develops to initial endocrine therapy. The National Comprehensive Cancer Network clinical practice guidelines for invasive breast cancer recommend AIs (tamoxifen or toremifene), fulvestrant, megestrol, fluoxymesterone, and estradiol as options for second-line therapy.[57] Thus, clinicians must decide which sequence of therapies to use for individual patients based on multiple patient-specific factors, such

as tumor characteristics (eg, human epidermal growth factor receptor 2 [HER2] status), burden of disease (eg, sites of metastases, symptoms), convenience of administration, and history with prior endocrine agent(s) with respect to MOA, duration of response, and time to disease progression.[56] In addition—and apart from clinical efficacy—tolerability, safety, and quality of life are also important factors to consider when sequencing the various endocrine therapies. When selecting a second-line endocrine therapy for patients with HR+ MBC, it is important to consider both how the MOAs of available endocrine therapies differ as well as the potential mechanisms of resistance to endocrine therapy.

Acquired resistance to endocrine therapy

Although the exact mechanisms of acquired resistance to endocrine therapy are unknown, they are likely linked to the MOA of the endocrine agent. A significant amount of laboratory research has identified numerous potential molecular mechanisms of acquired resistance, which fall under several major categories: (1) estrogen hypersensitivity; (2) ER status modifications (eg, ER loss, mutation,

TABLE 1

Molecular mechanisms of resistance to endocrine therapies in breast cancer

Mechanism of resistance	Aromatase inhibitors	SERMs	SERDs
Estrogen hypersensitivity	✓	✓	
Loss of estrogen receptor α	✓	✓	✓
Mutated estrogen receptor α		✓	
Estrogen receptor β expression		✓	
Lack of progesterone receptor		✓	
Drug metabolism		✓	
Coactivator/corepressor expression		✓	
Increased growth factor signaling	✓	✓	✓
Increased estrogen receptor sensitivity	✓		

SERMs = selective estrogen receptor modulators; SERDs = selective estrogen receptor downregulators.
Source: Zilli et al[19]; Hurvitz and Pietras[58]; Dowsett et al[69] Reprinted from Zilli M, Grassadonia A, Tinari N, et al. Molecular mechanisms of endocrine resistance and their implication in the therapy of breast cancer. Biochim Biophys Acta 2009;1795:62–81, Copyright 2009, with permission from Elsevier.

or change in gene expression); (3) changes in the intracellular molecular environment (eg, loss of PgR, changes in expression of cofactors); and (4) increased growth factor signaling and crosstalk between the ER and growth factor signaling pathways.[19] Some of these mechanisms contribute to resistance to all endocrine agents, whereas other mechanisms are specific to a particular agent (Table 1).[19]

Estrogen hypersensitivity, the ability of cells to grow in the presence of low levels of estrogen, is a major mechanism by which breast cancer cells become resistant to endocrine therapy in the presence of long-term estrogen deprivation (LTED).[19,60] In preclinical models of estrogen hypersensitivity, breast cancer cells function and retain ER signaling in the presence of estrogen concentrations up to 10,000 times lower than normal by upregulating ER expression and expression of other estradiol-stimulated genes.[61] This hypersensitivity is thought to explain why some patients develop resistance to tamoxifen or AIs after long-term treatment.[60,61] Notably, a preclinical study showed that treatment with fulvestrant, but not tamoxifen, inhibited the growth of breast cancer cells resistant to LTED.[62]

Several studies also suggest that low-dose estrogen (LDE) can be used to overcome estrogen resistance.[58,63] Preclinical investigation suggests that LDE treatment may revert resistant tumors back to a sensitive state.[58] Experiments with tamoxifen-resistant breast cancer cell lines showed that treatment with LDE enabled cells to regain susceptibility to tamoxifen as well as AIs and fulvestrant.[63]

The second mechanism of endocrine resistance is alteration in ER expression (eg, increased/decreased expression of ERα or ERβ, or ER mutations).[19] Abnormal DNA methylation or increased histone deacetylation has been associated with ER-negative status in breast cancer; as a result, agents that inhibit DNA methylation and histone deacetylation are being explored. Mutations in ER-producing nonfunctioning receptors have been found in patients with tamoxifen-resistant breast cancer, but they are not common.[19,54] In contrast, loss of ER expression is a key mechanism thought to play a role in the development of acquired resistance to fulvestrant in HER2-positive tumors.[19]

Results from laboratory experiments and retrospective clinical studies suggest that increased growth factor signaling and modifications in the expression of coregulatory molecules (coactivators and corepressors) may contribute to the development of resistance to endocrine therapies.[19,54] For example, the overexpression of the coactivator amplified in breast cancer, AIB1, has been associated with a poorer prognosis in patients treated with tamoxifen for HER2-positive or HER3-positive breast cancer.[64–66] Also, endocrine resistance has been reported in vitro when cells express low levels of ER corepressors such as the nuclear receptor corepressor 1 (NCOR1), which can bind to ERs and inhibit partial agonist activity of tamoxifen.[19] As a result, low NCOR1 mRNA expression correlates with shorter relapse-free survival and may be an independent predictor of tamoxifen resistance.[67,68]

ER signaling participates in an autocrine signaling loop with epidermal growth factor receptor (EGFR) and HER2 to regulate cellular proliferation.[19] Suppression of ER by endocrine therapies increases the expression of EGFR and HER2, activating downstream MAPK/AKT signaling cascades, which result in proliferative effects that counter the antitumor effects of endocrine therapy. Thus, increased signaling by HER2-regulated pathways is an important contributor to intrinsic and acquired endocrine resistance in breast cancer.[69,70]

Also, in the absence of estrogen, the AF-1 domain of ERs can be activated by the MAPK, PI3K, or other signaling pathways that are triggered by crosstalk with activated EGFR and insulin-like growth factor receptor 1.[19,70] Growth factor receptor crosstalk is thought to be important in the development of resistance to tamoxifen in ER-positive tumors because this agent does not inhibit AF-1 transcriptional activation.[19]

Future directions

Developing endocrine-based combination therapies

The low toxicity and differing MOAs of endocrine therapies pro-

vide a rationale to develop combination endocrine therapies. However, this approach has had mixed success in both preclinical and clinical studies. In a mouse breast cancer model, the combination of letrozole with tamoxifen did not produce a better antitumor response than either agent alone.[71–73] In contrast, in the same tumor model, the combination of exemestane and tamoxifen was more effective in reducing tumor growth compared with either agent alone.[74] Although some investigators have reported an additive effect in vivo when an AI or tamoxifen was combined with fulvestrant,[75,76] others have found that these combinations were no more effective than the AI alone.[71,72] It should be noted that the combination arm in the phase III ATAC study was quickly discontinued because of lack of efficacy at 33 months of follow-up.[77] Thus, despite a strong rationale for using an AI in combination with tamoxifen, the data are largely conflicting and likely require further study.

Some of these endocrine combination therapies are being tested in clinical trials. The FACT phase III randomized study showed no improvement in clinical benefit with the addition of a fulvestrant loading dose (LD; administered at 500 mg on day 0, 250 mg on day 14, 250 mg on day 28, and then 250 mg monthly) to anastrozole compared with anastrozole alone at first relapse in postmenopausal women with HR+ ABC.[78] Results from two additional phase III studies are pending. The first, SWOG-S0226,[79] is comparing anastrozole with anastrozole plus a fulvestrant LD as first-line therapy in postmenopausal women with MBC, and the second, SOFEA,[80] is comparing a fulvestrant LD with or without anastrozole versus single-agent exemestane in postmenopausal women with ABC or MBC following disease progression on nonsteroidal AIs.

Preclinical studies also provide a rationale for combining endocrine therapy with signal transduction inhibitors such as the dual EGFR/HER2 tyrosine kinase inhibitor lapatinib (Tykerb), the anti-HER2 monoclonal antibody trastuzumab (Herceptin), the antivascular endothelial growth factor monoclonal antibody bevacizumab (Avastin), and the mammalian target of rapamycin inhibitor temsirolimus (Torisel).[81] Certain interesting combinations are currently in phase III studies, and so far, they have shown excellent efficacy at the cost of higher toxicities. Results from the recently completed TAnDEM study showed improved PFS with anastrozole plus trastuzumab compared with anastrozole alone in postmenopausal women with HER2+ and HR+ MBC; however, the number of adverse events and serious adverse events was considerably higher in the combination arm.[82]

In another phase III randomized study, the addition of lapatinib to letrozole significantly improved PFS and clinical benefit compared with letrozole alone as first-line therapy for women with HR+ MBC.[83] Grade 3 or 4 adverse events were more common in the letrozole plus lapatinib arms than in the letrozole monotherapy arm. An ongoing four-arm phase III study is comparing fulvestrant versus fulvestrant plus an AI (exemestane, anastrozole, or letrozole), versus fulvestrant plus lapatinib, versus fulvestrant plus an AI plus lapatinib in postmenopausal women with MBC after disease progression with a previous AI.[84]

Identifying the molecular drivers of breast cancer

In addition to clinical investigations to improve combination therapy, preclinical research is also needed to further understand the molecular drivers of breast cancer growth and metastasis. Although progress has been made, much remains to be learned to clarify the networked re-dundancy of resistance pathways that breast tumors enlist to counter endocrine therapies.

In addition to the molecular complexity of endocrine intracellular signaling and crosstalk with growth factor receptor pathways, treatment of patients must contend with the influence of heterogeneity within individual tumors and among the primary tumor, locally recurrent tumors, and metastatic sites. Results from numerous studies indicate that therapeutic targets in breast cancer (ie, ER, PgR, HER2) identified in primary tumors and some metastatic sites are not necessarily homogeneously expressed.[85–89] One study reported discordance rates between primary and recurrent breast cancer of 18% for ER, 40% for PgR, and 14% for HER2.[87] Another study reported discordance rates of 18% for ER, 42% for PgR, and 7% for HER2 between primary and metastatic sites and of 13% for ER, 33% for PgR, and 2% for HER2 between primary and locally recurrent lesions.[86] These data emphasize the need to evaluate ER, PgR, and HER2 status at local sites of recurrence as well as distant metastases to improve treatment planning.

To further complicate matters, with the development of microarray technology, some degree of intratumor heterogeneity in ER and PgR expression has been found in biopsy samples from breast cancer patients.[90,91] Initial evidence suggests that this heterogeneity may have a significant impact on clinical outcomes.[90]

Conclusions

Although there has been substantial success in using endocrine therapy for HR+ breast cancer over the past 2 decades, a large percentage of patients eventually develop resistance and experience disease progression. Resistance, whether intrinsic or acquired, often involves crosstalk between estrogen and growth factor receptors or is related to the effects of LTED.

These effects may ultimately lead to a hypersensitive effect of estrogen- or ligand-independent activation of estrogen signaling.

Because the mechanisms of resistance to endocrine therapy are thought to be related to the MOA of each agent, it is important to understand the distinct mechanistic properties of AIs, tamoxifen, and fulvestrant. Compared with the AIs, which inhibit the production of estrogen, tamoxifen and fulvestrant work by binding to and inhibiting ER signaling. However, despite some similarities in the MOAs of tamoxifen and fulvestrant, a number of key mechanistic differences exist between these agents with respect to effects on AF domains, ER homodimerization, ER degradation, and inhibition of nuclear translocation. The prediction and management of resistance to therapy are under investigation, and it is hoped that an enhanced understanding of the MOAs of antitumor agents, as well as the estrogen signaling process, will enable the further delay of breast cancer disease progression using the most effective sequence of endocrine therapies for each patient.

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