Hormonal Modulation in the Treatment of Breast Cancer

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- Ovarian suppression
- GnRH agonist
- Antiestrogens
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- SERD

**BREAST CANCER EPIDEMIOLOGY**

Breast cancer is the most commonly diagnosed malignancy in women worldwide. It is estimated that 207,090 women were diagnosed with and 39,840 women died of breast cancer in 2010. Surveillance, Epidemiology and End Results data predict that 12\% of women born today, or 1 in 8 women, will be diagnosed with breast cancer in their lifetime. Long-term survival rates are closely linked to breast cancer stage at presentation. Sixty percent of women are diagnosed when the cancer is confined to the breast (without lymph node involvement), and these women have an excellent 5-year relative survival of 98\%. Thirty-three percent of women with breast cancer present with disease that has spread to local/regional lymph nodes and for this group, 5-year relative survival is 83.6 \%. Only 5\% of women with breast cancer present with initial metastatic disease, and for this population 5-year relative survival is only 23.4\% and close to none are cured of the cancer.\textsuperscript{1}

Breast cancer can metastasize many years after the initial diagnosis and treatment. Thus, the 5-year relative survival statistics omit recurrences that occur after 5 years, which is more common in women treated with adjuvant chemotherapy, trastuzumab, or hormonal modulation than in most other cancers. Furthermore, most of these relapses are outside the breast, leading to incurable stage IV disease. Despite recent advances in breast cancer therapy and earlier diagnosis with screening, 24\% to 30\%
of women with node-negative disease at diagnosis will eventually experience a disease recurrence, and 40% to 80% of women with node-positive disease will experience relapse. When distant metastases occur, the prognosis is poor, with a median survival of 18 to 36 months from time of recurrence. Thus, an urgent need still exists to improve curative treatments for women with breast cancer and to improve efficacy of treatment for women with metastatic disease.

Metastatic relapse is generally explained by the theory that many women with primary breast cancer have subclinical metastases at presentation. Surgery and radiotherapy are targeted at removing the primary tumor and preventing local relapse, while systemic treatments including chemotherapy, hormonal modulation, and Her-2 targeted immunotherapy, are directed at eliminating micrometastases. Systemic treatments given before surgery are called neoadjuvant therapy and those given after surgery are called adjuvant therapy.

In the United States and Canada, breast cancer incidence has recently leveled off and even decreased slightly in age groups older than 45 years. One theory attributed the decline in incidence to the reduced use of hormone replacement therapy (HRT) after the Women’s Health Initiative study showed HRT increased incidence of breast cancer and failure to prevent cardiac and thrombotic events.

**ESTROGEN RECEPTOR EXPRESSION AND HORMONAL MODULATION IN BREAST CANCER**

Seventy percent of breast cancers express the estrogen receptor (ER) and usually have a lower-grade phenotype than ER-negative cancers. During the first several years after diagnosis, patients with ER-positive tumors tend to have a lower recurrence rate than those with ER-negative tumors. The recurrence rate of ER-positive tumors remains stable through years 6 or 7 and drops thereafter. Most importantly, ER status is an important predictor of the likelihood of response to endocrine therapies. In patients with localized disease, adjuvant hormonal modulation is used for 5 to 10 years to reduce the risk of distant recurrence. When metastases occur in women receiving an adjuvant therapy, tumors are likely to have primary or acquired resistance to that agent.

Although many laboratories have described mechanisms of resistance to endocrine therapies, none of these mechanisms have been clinically validated to guide treatment decisions. Thus, the choice of an adjuvant hormonal agent depends entirely on the patient’s menopausal status; women with intact ovarian function receive selective estrogen receptor modulators (SERMs) and postmenopausal women receive aromatase inhibitors (AIs).

Women with metastatic breast cancer require treatment for the duration of their lives. In this setting, hormonal therapy is used to slow tumor progression. Hormonal modulation is highly effective and less toxic than chemotherapy. However, in this population a significant portion of ER-positive tumors will not respond to antiestrogen therapy initially, and most that do respond will ultimately develop resistance. Once the tumor becomes resistant to therapies to which it has been exposed, cytotoxic chemotherapy is required. Both primary and acquired resistance to endocrine therapy underscore the need to develop new treatments and to better tailor which treatments are chosen for which tumors.

This article explores the history of endocrine therapy for the treatment of breast cancer, the clinical evidence behind the current standards of care and controversies that may change these standards in the future.
Earlier Methods of Hormonal Modulation and Their Current Use

Ovarian suppression and ablation

Recognition of the relationship of ovarian function to breast cancer was first noted when Albert Schinzinger proposed surgical oophorectomy as a treatment for breast cancer in 1889.\(^6\) He observed that the prognosis for breast cancer was better in older women than in younger women and reasoned that oophorectomy would make younger women prematurely old, causing atrophy of the breast and the cancer.\(^7\) Despite Schinzinger's intellectual contribution, Beatson\(^8\) was the first to use ovarian ablation to treat advanced breast cancer in 1896. The first randomized trials of ovarian ablation in the adjuvant setting began in 1948.\(^9\)

Several methods of ovarian ablation or ovarian suppression are available. Surgical oophorectomy causes a permanent reduction in ovarian steroid production. In women with BRCA1 or BRCA2 mutations, surgical oophorectomy leads to a 50% reduction in breast cancer incidence and a 95% reduction in ovarian cancer. Radiation-induced ovarian ablation can be accomplished using a variety of fractionation schedules, ranging from 4.5 Gy in 1 fraction to 20 Gy in 10 fractions.\(^10\)

Pharmacologic ovarian suppression is accomplished with gonadotropin releasing–hormone (GnRH) agonists, such as goserelin and leuprolide. Mechanistically, both of these agents mimic the hypothalamic hormone GnRH. In normal physiology, GnRH signals the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn stimulate ovarian steroid hormone production. Unlike endogenous GnRH, synthetic GnRH agonists have substitutions in the sixth and ninth terminal amino acids, which increase lipophilicity and render them long-acting. When first given, GnRH agonists are stimulatory and can cause a flare phenomenon. However, after 10 to 14 days, the continuous action leads to downregulation of GnRH receptors, which ultimately decreases production of LH and FSH and medical castration. Menopausal side effects are reversible when the GnRH agonists are cleared.

The meta-analysis conducted by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) in 2005 compared treatment with and without ovarian suppression and ablation in nearly 8000 women younger than 50 years.\(^11\) Results showed that ovarian ablation reduced the 15-year probability of breast cancer recurrence and mortality. The benefit was much larger in women who did not receive any additional adjuvant treatment. One possible reason for this is that women who undergo chemotherapy often develop ovarian failure, thus attenuating any additional benefit seen from ovarian suppression or ablation.

Although multiple studies have shown that ovarian suppression or ablation is preferable to no adjuvant treatment in premenopausal women with breast cancer, long-term follow-up from the four-arm prospective Swedish ZIPP trial (Zoladex in Premenopausal Patients), which randomized patients to: no hormonal modulation, ovarian suppression with goserelin alone, tamoxifen alone, or the combination of goserelin and tamoxifen, showed that, individually, goserelin and tamoxifen offered similar benefit to no adjuvant endocrine therapy, but the combination was not superior to either modality alone.\(^12\)

AIs act by inhibiting the production of estrogen in peripheral tissues and thus are only active in postmenopausal women who do not have an ovarian source of estrogens. Since 2003, when adjuvant AIs were shown to be more effective than tamoxifen in postmenopausal women, the question of whether premenopausal women should receive ovarian suppression and an AI rather than tamoxifen alone has generated increasing debate. This question will be answered by the three-arm SOFT trial, which is comparing 5 years of tamoxifen alone, 5 years of ovarian suppression combined
with tamoxifen, and 5 years of ovarian suppression with exemestane (a steroidal AI). However, induction of menopause is accompanied by a host of side effects, including hot flashes, changes in sex drive, vaginal dryness, loss of vaginal elasticity, dyspareunia, osteoporosis, sleep-cycle disturbance, and sometimes depression and anxiety. Therefore, unless the SOFT trial shows a benefit for ovarian suppression, tamoxifen alone will remain the standard of care for premenopausal women.

**High-dose estrogen** High-dose estrogen was the preferred endocrine treatment in postmenopausal women with advanced breast cancer before the introduction of tamoxifen in the 1970s. In 1979, Smith and colleagues concluded that high-dose estrogen in the form of Premarin improved survival in postmenopausal women with advanced breast cancer. In 1981, a trial performed by Ingle and colleagues concluded that the response rates between tamoxifen and diethylstilbestrol were similar, but that tamoxifen had significantly lower rates of thromboembolic disease. Based on tamoxifen’s improved toxicity profile, high-dose estrogen therapy was abandoned.

Use of high-dose estrogen is now being revisited. One hypothesis suggests that in patients who have been exposed to long-term estrogen deprivation as a result of AI therapy, the estrogen dose–response curve shifts to the left, with cancer cells showing increasing sensitivity to the toxic effects of estrogen. A recent phase II study showed a clinical benefit rate of 29% with 6 mg of daily estradiol in 66 patients with AI-refractory metastatic breast cancer.

**Megestrol acetate** The use of megestrol acetate (MA), an orally active synthetic derivative of progesterone, was first reported in breast cancer by Ansfield and colleagues in 1974. Its mechanism in the treatment of advanced breast cancer is unclear. In the 1980s, several trials showed that the response rate to MA was comparable to that observed with tamoxifen in postmenopausal women with metastatic breast cancer but was associated with an increased risk of thromboembolic events. Today, MA is only used in metastatic disease refractory to multiple lines of endocrine therapy.

**SERMs**

The SERMs, tamoxifen and toremifene are hormonal agents that compete with estradiol for binding to ERs. In breast tissue, this blocks the ability of ERs to act as transcription factors and inhibits estrogen-dependent cell proliferation and mammary tumor growth. Although both of these drugs display estrogen antagonist activity in breast and on breast cancer cells, they have estrogenic agonist activity on the endometrium, bone, and coagulation system. Tamoxifen has been a critical component in the treatment of breast cancer for more than 30 years and has served as the gold standard against which newer endocrine therapies were compared. Although it is highly effective for prevention and treatment of breast cancer, it is accompanied by a small but definitive increased risk of endometrial cancer and thromboembolic disease.

**TAMOXIFEN STUDIES**

Tamoxifen was initially developed in 1966 in Great Britain as an infertility agent. It was also found to suppress carcinogen-induced rat mammary tumors. The first clinical trial of tamoxifen was published in 1971. It was then studied in the United States, and was approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic breast cancer in postmenopausal women in 1977.

The role of tamoxifen in the adjuvant setting has been widely established. Results from 15-year follow-up from the EBCTCG/Oxford Overview showed that tamoxifen...
reduced the annual recurrence rate by 41% and the overall mortality rate by 34% in women with ER-positive breast cancer. Furthermore, adjuvant tamoxifen taken for 5 years after primary therapy also reduces the incidence of contralateral breast cancer by 47%.

From the 1970s until 2002 when anastrozole was approved, tamoxifen was the first-line endocrine therapy for localized and metastatic breast cancer in both premenopausal and postmenopausal women. It remains the mainstay of treatment for premenopausal women in both the adjuvant and metastatic setting.

In 1998, the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 trial showed that tamoxifen has a role in preventing breast cancer in women at increased risk for the disease. Among 13,388 women randomized to receive either tamoxifen or placebo, tamoxifen was shown to decrease the relative risk of invasive breast cancer by 49%. The benefit was especially strong for patients with a history of lobular carcinoma in situ (56% reduction) or atypical ductal hyperplasia (86% reduction). Very small but statistically significant increases were seen in the risk of endometrial cancer and thromboembolic events.

The following year, the NSABP B-24 study established the benefit of tamoxifen in the management of patients with preinvasive breast cancer, or ductal carcinoma in situ (DCIS). Women who underwent surgical resection followed by radiation were then randomized to tamoxifen for 5 years or placebo. A reduction in new breast cancer events was seen (invasive and DCIS), from 13% in the placebo arm to 8% in the tamoxifen arm. These results were recently confirmed in long-term follow-up from the UK/ANZ trial, which showed a reduction in the risk of ipsilateral recurrence by 22% and contralateral cancers by 56%.

TOREMIFENE

Toremifene, a SERM with a mechanism similar to that of tamoxifen, is used more commonly in Europe. Structurally, it has estrogenic and anti-estrogenic properties, but compared with tamoxifen, seems to exhibit less of a proliferative effect on the uterus. In a phase III randomized clinical trial of 217 post-menopausal women with ER positive advanced breast cancer, toremifene was compared with tamoxifen. A response rate of 64% was observed in the toremifene group as compared with 52% in the tamoxifen group.

Toremifene has also been studied in the adjuvant setting for perimenopausal and postmenopausal women with early-stage breast cancer, but is not FDA-approved for this indication. The combined analysis from the International Breast Cancer Study Group Trials 12-93 and 14-93 randomized 1035 perimenopausal and postmenopausal women with node-positive breast cancer to either toremifene or tamoxifen. Toremifene and tamoxifen yielded 5-year disease-free survival rates of 72% and 69%, respectively, and 5-year overall survival rates of 85% and 81%, respectively. Although these data suggest that toremifene could have a role in the adjuvant setting, heterogeneity existed between the study populations in both trials, and the FDA did not allow combined analysis. Unfortunately, each individual study was underpowered to show efficacy.

RALOXIFENE

Raloxifene is a SERM that is approved for the treatment of osteoporosis and as prevention of invasive breast cancer in postmenopausal women. The MORE trial was designed to examine the effect of raloxifene on osteoporosis fracture risk, with breast cancer incidence as a secondary end point. Raloxifene showed a 72% risk
reduction in breast cancer incidence; 93 osteoporotic women would need to be
-treated with raloxifene for 4 years to prevent one case of invasive breast cancer.\textsuperscript{33}

Subsequently, the STAR trial was designed to compare raloxifene with the gold
standard tamoxifen for preventing breast cancer in postmenopausal women.\textsuperscript{34} The
study showed equivalent numbers of invasive breast cancers in both arms, suggesting
equivalent chemoprevention benefit. Patients treated with raloxifene had fewer cases
of endometrial carcinoma and fewer thromboembolic events than those treated with
tamoxifen. Raloxifene has not been studied in premenopausal women or in women
with a history of DCIS or invasive breast cancer, and therefore is not appropriate for
these populations.

**FULVESTRANT**

The steroidal estrogen receptor downregulator fulvestrant is the first pure ER antago-
nist with no known agonist effects. It competitively and irreversibly binds the ER with
an affinity 100 times stronger than tamoxifen, and leads to its rapid degradation.\textsuperscript{35} As
a result, the ER is sequestered away from DNA, blocking its function as a transcription
factor and inhibiting the activation of downstream estrogen receptor–dependent
genes. Fulvestrant is given through intramuscular injection once every 4 weeks and
is FDA-approved for the treatment of postmenopausal women with metastatic,
hormone receptor–positive, advanced breast cancer that has progressed on a prior
hormonal therapy. Despite the FDA indication for second-line treatment, recent data
shows that fulvestrant is more effective than the AI anastrozole as first-line therapy
for metastatic breast cancer.

Two phase III trials (Table 1)\textsuperscript{36–38} compared the time to disease progression for ful-
vestrant (250 mg intramuscular injection monthly) to anastrozole (1 mg orally daily) in
851 postmenopausal women with advanced breast cancer whose disease had pro-
gressed on adjuvant hormonal therapy or first-line endocrine therapy in the metastatic
setting (96.5% of whom received tamoxifen). These studies showed that fulvestrant
was equivalent to anastrozole in the second-line treatment of metastatic breast

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<td><strong>A comparison of fulvestrant to anastrozole in advanced breast cancer from two phase III trials</strong></td>
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*Abbreviations: CR, complete response; PR, partial response; RR, relative risk; SD, stable disease; TTP, time to disease progression.*
cancer. Fulvestrant was well tolerated and was associated with a significantly lower incidence of joint disorders.

Investigators in these early fulvestrant trials observed that a significant number of patients in the fulvestrant arm experienced early disease progression. In addition, pharmacokinetic studies performed in early fulvestrant trials showed that it can take 3 to 6 months to achieve steady state blood levels. Thus, investigators postulated that achieving steady state levels earlier might enhance the efficacy of fulvestrant. Loading and high-dose fulvestrant regimens were subsequently developed.

The CONFIRM trial showed that 500 mg of fulvestrant given on day 1, 14, 28, and then every 28 days thereafter was superior to the FDA-approved 250-mg dose. These findings led to FDA approval of the 500-mg fulvestrant dose in 2010. Later that year, updated results from the FIRST trial, which compared 500 mg of fulvestrant with anastrozole in the treatment of first-line metastatic disease, were presented at the 33rd annual San Antonio Breast Cancer Symposium. Median time to disease progression was 23.4 months for fulvestrant versus 13.1 months for anastrozole, corresponding to a 35% reduction in risk of progression. Thus, when optimally dosed, fulvestrant seems to be superior to anastrozole in the treatment of first-line metastatic disease.

Although fulvestrant is not approved for use in premenopausal women, no mechanistic reason exists why it should not work in this population. One study randomized premenopausal women with ER-positive tumors to a single 750-mg intramuscular dose of fulvestrant or a daily 20-mg dose of tamoxifen for 14 to 16 days in the period between initial biopsy and surgery. The drugs reduced the proliferative index (Ki-67) and downregulated ER expression equivalently, but only fulvestrant led to downregulation of the progesterone receptor (often used a marker to show downstream efficacy of ER inhibition). Although this study was not designed to show long-term clinical efficacy, results suggest that fulvestrant has biologic activity in this population. Phase I trials to find the optimal long-term dose in premenopausal women have not been performed.

RESISTANCE TO TAMOXIFEN

Multiple biologic factors predict resistance to tamoxifen, including overexpression of cyclin D1, underexpression of CDK10, and overexpression of coactivator AIB1, and possibly Her-2/neu overexpression (see the article by Doris Germain elsewhere in this issue for further exploration of this topic). Despite a large body of research enumerating mechanisms of tamoxifen resistance, none of these are used clinically because of the limited treatment options for women with preserved ovarian function. When adjuvant tamoxifen treatment fails and distant recurrences occur, the impact on quality and quantity of life is devastating. Thus, one must ask whether better treatment alternatives are available for premenopausal women whose tumors have characteristics that predict resistance to tamoxifen therapy. The SOFT trial will address whether premenopausal women with breast cancer should receive ovarian suppression and/or AIs. However, it will not address whether other non-menopause-inducing agents, such as fulvestrant, could be used in premenopausal women with tumor characteristics predictive of tamoxifen resistance. The authors of this article are actively pursuing this area of research.

The past several years has seen an intense interest in the role of hepatic CYP2D6 enzyme genetic variants and clinical outcome in women treated with tamoxifen. In the United States, 10% to 20% of the population have genetic variants of the CYP2D6 enzyme, which ineffectively metabolize tamoxifen to its active metabolite endoxifen. In 2005, a widely publicized study by Goetz and colleagues correlated
CYP2D6 genotype with clinical outcome in 213 women treated with adjuvant tamoxifen, and concluded that those who were poor metabolizers had a hazard ratio for recurrence four times that of those who were extensive metabolizers. Since this publication, clinical testing of CYP2D6 spread rapidly before any clear data were available on how to integrate the results into clinical practice. Confounding the issue more, in late 2010, data correlating clinical outcome and CYP2D6 genotype in two large prospective studies on adjuvant hormone treatment were presented at the 33rd annual San Antonio Breast Cancer Symposium. Clinical outcomes from the ATAC trial in 588 genotyped women and the BIG 1-98 trial in 1243 genotyped women did not correlate with presence of the CYP2D6 variant in either the tamoxifen or the AI arms. These groups of women are the largest prospectively treated populations studied thus far. Thus, data currently do not support making clinical treatment decisions based on CYP2D6 genetic variants, and testing outside of research should not be routinely offered to the general population taking tamoxifen.

One possible exception is women taking potent CYP2D6 inhibiting medications, which have been shown to lead to lower levels of endoxifen. Fluoxetine, paroxetine, bupropion, and duloxetine are potent inhibitors of CYP2D6. Citalopram, escitalopram, desvenlafaxine, and sertraline are weaker inhibitors of CYP2D6. In patients who require these medications, it may be warranted to check the genotype. Another option is to use venlafaxine in patients treated with tamoxifen, because it does not interfere with CYP2D6 metabolism.

**AIs**

In postmenopausal women, the main source of estrogen production occurs in the peripheral tissues (adipose, liver, skin, muscle, and breast tissue), where androstenedione is converted into estrone and estradiol. The final step is catalyzed by the enzyme aromatase. The AIs anastrozole, letrozole, and exemestane inhibit the conversion of androstenedione into estrogens, and lower circulating estradiol levels. These drugs do not work in premenopausal women because of high levels of ovarian estrogen production.

AIs are now the mainstay of treatment in postmenopausal women in both the adjuvant and metastatic settings. Numerous trials have shown moderately improved efficacy over tamoxifen, with significantly lower rates of serious side effects, including endometrial carcinoma and thrombosis (deep vein thrombosis, pulmonary embolism, and cerebrovascular accident). A classwide effect of the AIs is higher incidence of osteoporotic fractures. Additionally, at least 5% of women develop diffuse joint pain. Two types of antiaromatase agents are available: the type I steroidal inhibitor exemestane and the type II nonsteroidal inhibitors anastrozole and letrozole. Thus far, all studies comparing one AI with another have shown them to be equivalent.

**AIs IN PATIENTS WITH METASTATIC BREAST CANCER REFRACTORY TO TAMOXIFEN**

AIs were first tested in postmenopausal women with metastatic breast cancer refractory to tamoxifen. Anastrozole was FDA-approved in 1996 based on two studies that showed it was more effective and less toxic than megestrol acetate. The following year, letrozole was approved for the same second-line indication. Exemestane was approved for patients refractory to tamoxifen in 2005.

**AIs IN FIRST-LINE METASTATIC BREAST CANCER**

In November of 2000, the *Journal of Clinical Oncology* published the results of two multinational randomized phase III trials comparing anastrozole with tamoxifen in
the first-line treatment of metastatic breast cancer in postmenopausal women. The North American study showed a significant increase in time to disease progression in the anastrozole arm (11.1 vs 5.6 months).\textsuperscript{53} Subsequent trials also showed that letrozole\textsuperscript{54,55} and exemestane\textsuperscript{56} were superior to tamoxifen in the first-line treatment of metastatic breast cancer.

**Als in the Adjuvant Setting**

Anastrozole was the first AI approved for the adjuvant treatment of breast cancer. The three-arm ATAC trial randomized more than 9000 women to 5 years of either tamoxifen, anastrozole or both.\textsuperscript{57,58} The 100-month analysis showed that anastrozole is more effective than tamoxifen, with an absolute improvement in disease-free survival of 2.5% at 5 years and 4.1% at 9 years in patients with ER-positive disease, and with lower rates of thrombotic complications and endometrial cancer\textsuperscript{59} (Fig. 1). A significant reduction in rates of contralateral breast cancer also occurred.

Letrozole was initially studied in the extended adjuvant setting. The MA 17 trial randomized more than 5000 women who had completed 5 years of treatment with tamoxifen to an additional 5 years of letrozole versus placebo.\textsuperscript{60} At 4-year follow-up, the letrozole group showed a 4.6% absolute benefit in disease-free survival. Subsequently, the BIG 1-98 trial showed that up-front letrozole is superior to up-front tamoxifen in hormone therapy–naïve patients (Fig. 2).

Exemestane was first studied in the adjuvant setting in women who had received 2 to 3 years of tamoxifen. The Intergroup Exemestane Study randomized women either to an additional 2 to 3 years of tamoxifen or to change to 2 to 3 years of exemestane. At 8-year follow-up, the group that was switched from tamoxifen to exemestane had an

![Fig. 1. Disease-free survival Kaplan-Meier curve for all patients randomized to anastrozole or tamoxifen monotherapy in the ATAC trial (intent to treat). (From DailyMed. Anastrozole tablet. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=19380.)](image-url)
absolute overall survival benefit of 2.4% and absolute disease-free survival benefit of 4.4%. Overall, these studies show that AIs are the first choice in the adjuvant treatment of postmenopausal women with endocrine-sensitive tumors. Thus far, all studies that have compared AIs have shown equivalence.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Hormonal modulation plays a key role in the primary prevention of breast cancer and in adjuvant and palliative therapy for metastatic disease. Tamoxifen remains the mainstay of treatment for premenopausal women, whereas AIs have come to dominate all realms of treatment for postmenopausal women. Several important questions remain. What is the optimal treatment for premenopausal women and should it include ovarian suppression? How can resistance to antiestrogen therapy be overcome? And perhaps most importantly, do biologic predictive factors exist that can be used to determine which endocrine therapy a patient should receive? The authors of this article believe that further studies are necessary to explore whether known markers of endocrine resistance can be used to predict clinical response. Their group is working to develop this personalized endocrine treatment.

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