Master of the Female Half-Length Figures, 1530. *Madonna and Child*. From the collection of Dr. Gordon and Adele Gilbert of St. Petersburg, Florida.

New Hormonal Therapies for Breast Cancer

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New hormonal treatments for breast cancer address more potent ways to inhibit estrogen receptor-mediated cancer progression pathways.

Background: *There has been an explosion in the development of hormonal therapies for the treatment of breast cancer. Several new agents have been approved for the treatment of breast cancer in the metastatic setting, and trials are ongoing in the adjuvant and prevention setting to improve hormonal therapy for the prevention and treatment of breast cancer.*

Methods: *The literature on new hormonal therapies for the treatment of breast cancer is reviewed, with an emphasis on newer agents.*

Results: *Two antiestrogens are now approved in the United States for the treatment of metastatic breast cancer. Other antiestrogens have activity in metastatic breast cancer as well as in osteoporosis. Newer pure antiestrogens may overcome resistance to tamoxifen. Several aromatase inhibitors are available for the treatment of metastatic breast cancer.*

Conclusions: *Many hormonal agents are now available for both adjuvant and advanced disease settings. Developments will depend on clarifying mechanisms of resistance to antiestrogens and identifying new classes of agents that lack cross-resistance to standard therapy.*

Introduction

Tamoxifen has been the preferred antiestrogen hormonal treatment for breast cancer for the last 30 years.[1] It is a nonsteroidal antiestrogen with tissue selective estrogen agonist and antagonist activity. Tamoxifen exerts beneficial estrogenic effects on bone density and serum lipids but unfavorable estrogenic effects in the endometrium.[2-4] The antiestrogen effects of tamoxifen in the breast led to its use in the treatment of breast cancer. It is the established therapy to consider in all stages of breast cancer. The finding of endometrial cancer resulting from tamoxifen treatment has led researchers to investigate new agents that retain favorable estrogenic properties in specific tissues and display antiestrogen activity on the endometrium. Such research has generated the concept of selective estrogen receptor modulators (SERMs) that mediate either estrogen agonist or estrogen antagonist effects in different tissues. The future of SERMs will depend on a better understanding of the various mechanisms of estrogen receptor (ER) modulation and whether they induce the wanted effects in specific tissues or organs.

There are at least two different types of ERs.[5] Alpha receptors predominate in the breast and uterus, and beta receptors predominate in the bone and blood vessels. In addition, many proteins interact with these receptors to act as coactivators or co-repressors at the receptors. To further complicate matters, at least 50 different transcription-activating factors modulate the effects of estrogen on its target genes.[5] The development of new therapies will be facilitated with a better understanding of the interactions of the ERs, coactivator and corepressor proteins, and transcription-activating factors. Agents should become available that specifically interrupt resistance pathways to standard hormonal treatment or bypass these pathways so that effective responses to therapy can be maintained. New developments are underway for both antiestrogen therapies and aromatase inhibitor therapies. Table 1 lists selected new agents in development. Some are approved for the treatment of metastatic breast cancer, and several are involved in ongoing studies in the adjuvant setting. Furthermore, some of these agents have not been developed primarily for treatment of breast cancer but are being investigated specifically for the prevention of the disease. The partial agonist/antagonist antiestrogen agents have added benefits of preventing osteoporosis and lowering lipid because of the estrogen agonist effects in these tissues. The aromatase inhibitors are not expected to provide these benefits. Compared with antiestrogens, however, they may provide a lower risk of thromboembolic events with no risk of added endometrial proliferation leading to endometrial cancer. To improve survival from breast cancer and other causes in the metastatic, adjuvant, and prevention settings, we now need to determine how best to use these new agents in terms of sequence and as single or combination drug therapies.

Table 1. — New Hormonal Therapies in Breast Cancer

	Nonsteroidal	Steroidal
Antiestrogens:	Toremifene (Fareston)	ICI 182,780 (Faslodex)
	Idoxifene	EM-800
	Droloxifene	
	TAT-59	
	Zindoxifene	
	Trioxifene	
	Raloxifene (Evista)	
Aromatase Inhibitors:	Anastrozole (Arimidex)	Formestane (Lentaron)
	Letrozole (Femara)	Exemestane

and other established estrogen-mediated risk factors such as age at first live birth, parity, and age of menarche. Women aged 35 to 65 years were randomly allocated to receive either tamoxifen 20 mg/day or placebo for 5 years. The results of this study indicate that tamoxifen reduced the incidence of breast cancer in this high-risk population by 49%.[8] The drug was well tolerated, and the dropout rate due to side effects was low. Other clinical endpoints included measures of bone fracture rate, cardiac mortality, endometrial cancer, and thromboembolic events. The increased rate of endometrial cancer was similar to that reported in breast cancer adjuvant treatment trials.[4,9] At 66 months of follow-up, the cumulative incidence of endometrial cancer was 13 per 1,000 women. There were no deaths from endometrial cancer in the tamoxifen treatment arm since these were early-stage tumors. Moreover, the incidence of bone fractures in the hip, spine, and lower radius was decreased by 19%, but thromboembolic events increased in women over 50 years of age. Cardiac mortality in the tamoxifen group was similar to that in the placebo group, but the study did not have the statistical power to show a difference in events that would have a significant impact on survival. As a result of this study, tamoxifen was approved in the United States for the prevention of breast cancer in women at increased risk of developing breast cancer. Before prescribing this drug to healthy women, the risks and benefits of tamoxifen should be discussed with them so that they are aware of possible effects.

New Antiestrogens

Toremifene

Toremifene is a chlorinated analogue of tamoxifen and has similar site-specific estrogen and antiestrogen activity.[10] Preclinical studies report that toremifene may result in less DNA adduct formation in the endometrium than tamoxifen.[11] DNA adduct formation is thought to be an important mediator of genetic changes and cellular progression to cancer.[12] However, toremifene has been shown to have comparable stimulatory effects as tamoxifen on human endometrial cancers in athymic mice.[13] Tomas and colleagues[14] investigated the effects of toremifene and tamoxifen on postmenopausal endometrium in breast cancer patients receiving therapy for 12 months. Parameters that included endometrial thickness, cellular proliferation, and uterine fibroids and polyps were similar in the two treatment groups. These data suggest that toremifene has estrogenic effects in the uterus that are comparable to tamoxifen and that toremifene may be associated with an increased risk of endometrial cancer. The actual incidence of endometrial cancer associated with toremifene treatment will be determined in the present ongoing adjuvant trials. Saarto and colleagues[15] have evaluated changes in lipid levels from toremifene and tamoxifen during the first year of use. Toremifene and tamoxifen produced similar changes with one exception: toremifene resulted in a rise in serum HDL levels by 14% compared to a 5% decrease in serum HDL levels in women taking tamoxifen. The significance of this finding is unclear. Following reports of several phase III trials demonstrating that toremifene is as efficacious as tamoxifen in the first-line treatment of metastatic breast cancer, toremifene was approved for the front-line treatment of metastatic breast cancer in ER-positive or ER-unknown patients. The Eastern European trial[16] and the Nordic trial[17] each included more than 400 postmenopausal women with metastatic breast cancer. The larger US trial,[18] which included 648 postmenopausal women with metastatic breast cancer, compared tamoxifen (20 mg/day) vs a standard dose of toremifene (60 mg/day) and a higher dose of toremifene (200 mg/day) and found a similar response rate (19.1% vs 21.3% vs 22.6%, respectively). Similarly, the Eastern European trial[16] tested two different dose levels of toremifene at 60 mg and 240 mg daily. Responses ranged from 30% to 37% with no statistically significant differences reported in response rates. In all three trials, overall response, median duration of response (16 to 26 months), and median survival (23 to 38 months) were not significantly different from those seen with tamoxifen. The most common adverse events (hot flashes, sweating, nausea and/or vomiting, vaginal discharge, dizziness, edema, vaginal bleeding, liver function abnormalities, ocular changes, and thromboembolic events) occurred with similar frequency with the two agents. To date, these phase III trials have not demonstrated greater benefit from higher doses of toremifene. Multiple phase II metastatic breast cancer trials investigating toremifene in tamoxifen-refractory patients demonstrate cross-resistance to tamoxifen based on low response rates. The largest of these trials reported by Vogel and colleagues found an overall response rate of 5%.[19-24]

Toremifene is now being compared with tamoxifen in adjuvant trials. The first adjuvant trial to open in 1992 was the Finnish trial,[25] which compared use of either toremifene 40 mg/day or tamoxifen 20 mg/day for 3 years in postmenopausal women with node-positive breast cancer. The results at three years of median follow-up demonstrate no significant differences in breast cancer recurrence rates and adverse events in the two treatment arms.[25] Other effects such as endometrial thickening, cytologic changes, DNA adduct formation, serum lipid levels, bone density changes, and ocular effects are being monitored to determine any potential benefits from toremifene compared to tamoxifen.

Idoxifene

Idoxifene is an antiestrogen in clinical development for several different treatment settings. It was designed with an iodine atom at the 4 position of tamoxifen to prevent metabolic activation to 4-hydroxytamoxifen and an additional pyrrolidine side chain to decrease carcinogenic potential associated with demethylation.[26] In animal models, idoxifene use decreased uterine weight, prevented bone loss, and lowered serum cholesterol levels.[27] Coombes and colleagues[28] reported on a phase I trial of idoxifene in 20 metastatic breast cancer patients who had previously been treated with tamoxifen. Using a dose between 10 to 60 mg orally per day, the drug was well tolerated with only mild toxicities, and the patients had a partial response rate and stable response rate of 14% and 29%, respectively, ranging from 1.4 to 14 months.

Droloxifene

Droloxifene is a monohydroxylated metabolite of tamoxifen. This 3-hydroxy-tamoxifen has some antiestrogenic effects in the uterus and maintains bone density in animal models.[29,30] There have been multiple phase II trials in metastatic breast cancer.[31-33] The largest was reported by Rauschning and Pritchard,[34] who investigated dosages of droloxifene ranging from 20 to 100 mg/day. Responses in the 269 women assessable for response revealed a 30% response in the 20-mg arm compared to a 47% response in the 40-mg arm and a 44% response in the 100-mg arm. Response rates favored higher doses (40 mg vs 20 mg: P=0.02; 100 mg vs 20 mg: P=0.04). The median response duration was 12 months in the 20-mg arm, 15 months in the 40-mg arm, and 18 months in the 100-mg arm. In all of these trials, droloxifene was well tolerated, and the side effects were similar to that of tamoxifen.

TAT-59

TAT-59 is a prodrug that requires dephosphorylation to become the active metabolite of tamoxifen, 4-hydroxytamoxifen. This agent has a high affinity for the ER.[35] A phase II trial has been reported in abstract form comparing the efficacy of tamoxifen with TAT-59 in the first-line treatment of metastatic breast cancer.[36] The response rate was assessed in 193 patients given 20 mg/day of either agent for more than 12 weeks. The total response rate was 30% in the TAT-59 arm compared to 26.5% in the tamoxifen arm. The responses, median duration of response, and survival were similar for both treatments. Adverse reactions were mild, and TAT-59 had comparable toxicities to tamoxifen.

Zindoxifene

Zindoxifene is an indole derivative of tamoxifen. A phase I/II trial of zindoxifene was reported by Stein and colleagues[37] from the United Kingdom. The doses ranged from 10 mg/day to 100 mg/day orally. Twenty-eight women with metastatic breast cancer who had previously received endocrine therapy were treated with no objective responses; 20% had disease stabilization for 5 months. Nausea was the dose-limiting toxicity in 50% of patients at a dose of 80 mg/day.

Raloxifene is a nonsteroidal benzothiophene derivative that binds to the ER and has been classified as a SERM because it has been shown to have antiestrogenic effects in the uterus and breast as well as estrogenic effects on bone and cholesterol.[39-42] A phase II trial was reported comparing the efficacy of raloxifene in metastatic breast cancer patients who were refractory to tamoxifen. A dose of 200 mg/day was chosen after reviewing data from phase I studies. The drug was given for up to 8 months; however, no objective responses were observed.[43] Because of the beneficial effects of raloxifene in bone density and serum lipids, raloxifene was studied in postmenopausal women with no history of breast cancer. The aim was to determine if raloxifene was a reasonable alternative agent for women who wished to avoid estrogen replacement therapy because of the potential increased risk of breast cancer. An osteoporosis prevention trial was initiated investigating raloxifene, and postmenopausal bone mineral density increased by by 2% to 3% compared to placebo after two years of use.[44] Raloxifene was approved in the United States for the prevention of osteoporosis in postmenopausal women after review of the data from three large multicenter trials (Eli Lilly Pharmaceuticals data on file, 1998). This antiestrogen also produced lipid profile changes similar to those with tamoxifen.[45] Raloxifene did not cause endometrial thickening or cellular proliferation and did not cause symptoms of estrogen effects on the endometrium such as vaginal bleeding.[44] The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was first reported at the American Society of Clinical Oncology (ASCO) meeting in May 1998. In this trial, 7,705 postmenopausal women with a history of osteoporosis were recruited. All patients received 1,200 mg/day of calcium and were allocated to receive raloxifene at 60 mg/day or 120 mg/day or placebo. At a median follow-up of two years, the incidence of vertebral fractures was reduced by 44% in the women taking raloxifene compared to placebo, and there was no difference in vertebral fractures in the standard vs high-dose raloxifene group.[46] The incidence of ER-positive breast cancer was 74% lower in the raloxifene group compared with the placebo group.[47] As in the tamoxifen breast cancer prevention trial (NSABP P-1), the protection was seen only in the group of women who developed ER-positive breast cancers. The incidence of endometrial cancer was not increased in either of the raloxifene treatment groups when compared to the placebo group. In fact, the incidence of uterine cancer was found to be 62% lower; however, this finding did not reach statistical significance (P=0.232).[47] These findings have prompted further investigation of raloxifene as a breast cancer preventive agent in a prospective fashion and in comparison to tamoxifen. Currently, there is no approved indication for raloxifene in the management of any phase of breast cancer. Use of raloxifene in the treatment of breast cancer should be restricted to participation in the NSABP P-2 breast cancer prevention trial.

New Pure Antiestrogens

Two steroidal antiestrogens have been developed that have pure antiestrogen activity in all tissues.[48,49] ICI 164,384 has been studied extensively in the preclinical setting; however, the more potent ICI 182,780 (Faslodex) is being studied in human clinical trials in metastatic breast cancer. Faslodex is not orally bioavailable and must be given intramuscularly on a monthly basis. An initial phase II trial in metastatic breast cancer [50] reported promising results in a tamoxifen-refractory population. This small trial of 19 women demonstrated that monthly administration of Faslodex at 250 mg intramuscularly provided a partial response rate of 37% and a stable disease response of 32% with a median duration of response of 26 months. Thus, a lack of cross-resistance with tamoxifen was apparent in 69% of the patients. Menopausal side effects did not appear to be increased by Faslodex therapy. Preclinical data demonstrated that Faslodex does not cross the blood-brain barrier and suggests that Faslodex might have fewer side effects in terms of menopausal symptoms than other antiestrogens.[49]

Another class of novel antiestrogen compounds inhibit estradiol-mediated action of the ERs. EM-652 is the active metabolite of the prodrug EM-800 and is available in oral form. Both are potent nonsteroidal pure estrogen antagonists of both alpha and beta ER subtypes.[51] EM-652 is 20 times more potent than Faslodex or droloxifene and is 400 times more potent than toremifene in displacing the 17 beta-estradiol from the rat uterine ER.[52] Thus, EM-652 has the highest known affinity to the ER when studied in competition receptor assays in animal models. No significant binding occurred to the rat uterine progesterone receptor. Preclinical studies have shown that EM-652 blocks *ras*-mediated induction of ER transcriptional activity that normally occurs in the presence of estrogen.[51] A small phase II trial is in progress in metastatic breast cancer to not only investigate the efficacy of EM-800, but also address the potential lack of cross resistance with tamoxifen because of its potent antiestrogen properties.

New Nonsteroidal Aromatase Inhibitors

Aromatase inhibitors have a different mechanism of action than antiestrogens and have been used primarily in the postmenopausal population. Aromatase is present in several peripheral tissues including the breast, muscle, liver, and adipose. Aromatase is important in the production of peripheral estrogen. The more important mechanism of action may be the intratumoral aromatase action.[53,54] The first aromatase inhibitor to become commercially available was aminoglutethimide. Aminoglutethimide has demonstrated activity in the metastatic breast cancer setting (response rates of 20% to 40%) when compared to established second-line therapy with megestrol acetate.[55-57] It produces effects on glucocorticoid production and is now used infrequently in the clinical setting due to side effects.

Two new aromatase inhibitors with more potent aromatase inhibition than aminoglutethimide — anastrozole and letrozole — are now approved in the United States for second-line treatment of metastatic breast cancer in postmenopausal women. Anastrozole and letrozole have been investigated in tamoxifen refractory patients. Ongoing trials are comparing these agents to tamoxifen as front-line therapy for metastatic breast cancer.

Anastrozole

Anastrozole is an achiral triazole derivative that is similar to aminoglutethimide.[58] However, unlike aminoglutethimide, anastrozole does not require supplementation with corticosteroid treatment because it is more selective for the aromatase enzyme and does not disrupt adrenal corticoid production.[59] Recently, data were pooled from two phase III trials of similar design and included 764 patients.[60] Postmenopausal women with metastatic breast cancer who had progressed on tamoxifen were eligible. Two different dose levels of anastrozole were tested. Anastrozole given at 1 mg/day and 10 mg/day was compared to standard-dose megestrol acetate (40 mg orally four times daily). The different treatment arms demonstrated no difference in response rate or time to disease progression. However, a benefit in terms of survival was seen in the anastrozole group compared to the group on megestrol acetate. At a median follow-up of 31 months, anastrozole demonstrated a statistically significant survival advantage over megestrol acetate (hazard ratio 0.78, P<0.025). The group using 10 mg/day showed no advantage in response rate or survival over the group using 1 mg/day. The median time to death in the 1-mg anastrozole, 10-mg anastrozole, and megestrol acetate groups were 26.7, 25.5, and 22.5 months, respectively. Overall, treatment with anastrozole was better tolerated than megestrol acetate, and the withdrawal rate due to adverse events was higher in the megestrol acetate group (4% vs 1.9%). Further analysis revealed that those patients who had a partial or complete response or who had stabilization of disease for at least six months had a longer time to disease progression in the anastrozole group than the megestrol group. The differences in time to disease progression in this subset of responders and the differences in withdrawal due to side effects are thought to account for the survival advantage seen in the anastrozole group.

Letrozole

Letrozole, a triazole derivative, was the next aromatase inhibitor to become commercially available. Two phase III trials involving postmenopausal women with metastatic breast cancer who had progressed or relapsed on tamoxifen have been published.[61,62] The first trial, which compared letrozole to megestrol acetate, showed an improved response rate and an improved time to treatment progression compared to the group receiving megestrol acetate.[61] The 2.5 mg/day dose of letrozole had a higher response rate (23.6%) than the 0.5 mg/day dose (12.8%). Time to progression and time to treatment failure were longer with the 2.5 mg/day dose of letrozole, and there was a suggestion of improvement in survival that did not reach statistical significance. The second trial, which compared letrozole to the first-generation aromatase inhibitor aminoglutethimide, showed a trend in favor of the 2.5 mg/day letrozole arm in overall response rate.[62] The overall survival was superior in the group that received 2.5 mg/day of

Table 2 compares the three third-generation aromatase inhibitors compared to megestrol acetate in terms of response rate and median overall survival as reported in each of the separate second-line metastatic breast cancer treatment trials that evaluated efficacy.

Table 2. — Results From Third-Generation Aromatase Inhibitors Used as Second-Line Treatment in Metastatic Breast Cancer*

	Anastrozole (1 mg) [60]	Letrozole (2.5 mg) [61,62]	Vorozole (2.5 mg) [63,64]
Number of Patients	764	551	452
Median Follow-up	31 months	33 months	NA
Response Rate (CR + PR)	12.6%	23.6% (*P*=0.04)**	9.7%
Median Duration of Response	NA	NR (*P*=0.02)**	18.2 months
Time to Progression	4.8 months	5.6 months	2.7 months
Median Survival Time	26.7 months	25.3 months	26 months
Overall Survival	HR 0.78 (*P*<0.02)**	HR 0.82 (*P*=0.15)	HR 1.06 (*P*=0.56)

* These agents have not been compared directly with each other. The results are from trials of each drug compared to megestrol acetate.

** Statistically significant.

CR = complete response
PR = partial response
HR = hazard ratio
NA = not available
NR = not reached

The steroidal aromatase inhibitors are exciting new agents because they appear to lack cross-resistance with the other nonsteroidal agents discussed above. These agents compete with the natural substrate for aromatase enzyme action and bind irreversibly to the enzyme leading to its inactivation.[65] This mechanism of action differs from anastrozole and letrozole, and these agents are quite specific because they bind to the active site of the enzyme.

Formestane

Formestane is now approved in Europe for the treatment of metastatic breast cancer in women who have failed tamoxifen therapy. Formestane is not orally bioavailable and is given intramuscularly each month. It has been tested in the front-line, second-line, third-line and even fourth-line setting in metastatic disease and has been shown to have high response rates. The response rate in the third- and fourth-line setting was 22% with a median response duration of 10 months. This result was surprising considering that this group of 147 women had previously failed multiple hormonal therapies including aminoglutethimide.[66] Further data from these trials include the lower rate of thromboembolic events associated with formestane in comparison to tamoxifen or megestrol acetate.[67]

Exemestane

The newest steroidal aromatase inhibitor to be developed is exemestane. This drug has been tested in metastatic breast cancer in the third-line treatment setting with similarly encouraging response rates as formestane. In a phase II trial of exemestane 25 mg/day given orally in postmenopausal women with metastatic breast cancer who had progressed on tamoxifen and megestrol acetate, the response rate was 11%. By including stabilization of disease for at least six months as a response category, the overall incidence of benefit increased to 29%. The median duration of effect, including stabilization of disease, was 11 months.[68] In another trial involving 241 postmenopausal women who had previously been treated with either aminoglutethimide, vorozole, or letrozole, the response rate, including stability of disease, after treatment with exemestane 25 mg/day was 25%.[69] Time to progression was 15 weeks. In the second-line treatment setting for metastatic breast cancer, exemestane 25 mg/day vs standard-dose megestrol acetate treatment in 128 postmenopausal women demonstrated a response rate of 28%. By including stabilization of disease for at least six months, the response rate increased to 47%. The median duration of response was 14 months.[70] These new data on the steroidal aromatase inhibitors suggest a lack of cross-resistance to tamoxifen and other nonsteroidal aromatase inhibitors.

Future Directions

Clinical trials are in progress evaluating new hormonal agents for the treatment and prevention of breast cancer. The new steroidal antiestrogens are under further clinical development in the metastatic setting. Faslodex (ICI 182,780) is being studied in several ongoing large phase III trials comparing its efficacy to anastrozole in the second-line treatment setting and in the first-line treatment setting with tamoxifen. A small, unpublished phase II trial investigating EM-800 in the metastatic breast cancer setting in women who had progressed on tamoxifen showed encouraging results and thus implies a lack of cross-resistance with tamoxifen. EM-800 will be studied in a large trial comparing its efficacy to anastrozole in the second-line treatment setting of metastatic breast cancer.

Adjuvant trials of hormone therapy are ongoing. The International Breast Cancer Study Group has opened two trials comparing the efficacy of tamoxifen to toremifene in postmenopausal and perimenopausal women given in combination or sequentially after adjuvant chemotherapy. A US trial for postmenopausal women has opened to compare the efficacy of tamoxifen with toremifene for the adjuvant treatment of early stage breast cancer. This trial excludes treatment with chemotherapy. The only premenopausal trial in progress compares the efficacy of tamoxifen to toremifene for five years given after four cycles of adjuvant chemotherapy with doxorubicin plus cyclophosphamide.

Several adjuvant trials are comparing the efficacy of various aromatase inhibitors with tamoxifen. Two large-scale trials using anastrozole are in progress. One study is comparing anastrozole plus tamoxifen vs each single agent for a five-year duration. The second involves studying two years of adjuvant tamoxifen, then three years of either tamoxifen or anastrozole. Letrozole is being studied in a similar fashion to anastrozole including a comparison of the efficacy of single-agent therapy and also an evaluation of sequential therapy. Patients who have taken tamoxifen for five years will receive letrozole or placebo for another five years. Finally, investigators are organizing a trial to evaluate tamoxifen treatment for two to three years followed by randomization to either tamoxifen or exemestane for a total of five years' duration of adjuvant therapy. These adjuvant trials will determine if these newer hormonal agents are superior to standard tamoxifen therapy or if a combination of agents is more effective than tamoxifen alone.

Conclusions

The burgeoning interest in the application of hormone therapy on preventing and treating breast cancer is being assisted by increasing understanding of the biologic processes that govern hormonal action. The advent of several new drugs bodes well for the future improvements in clinical outcomes from this clinical approach.

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