Review

Update on Endocrine Therapy for Breast Cancer

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Abstract

The choice of endocrine agent for breast cancer depends on the menopausal status of the patient, the stage of disease, prognostic factors, and the toxicity profile of the agent. Endocrine therapies are typically given sequentially, with the least toxic therapy given first. Tamoxifen is considered first-line endocrine therapy for all stages of breast cancer. New antiestrogens in development include nonsteroidal agents related to tamoxifen and pure steroidal antiestrogens. Luteinizing hormone-releasing hormone agonists are an effective form of endocrine therapy for premenopausal women with advanced breast cancer, and aromatase inhibitors are effective in postmenopausal women. Newer and more selective aromatase inhibitors that are p.o. active and have improved side-effect profiles have been developed. Recent trials have found these agents to improve survival in comparison to the progestins; thus, aromatase inhibitors are replacing progestins as second-line therapy for metastatic disease. Current trials are examining the potential role of aromatase inhibitors as first-line therapy for metastatic disease or as adjuvant therapy for early disease. The antiestrogens and antiandrogens studied thus far have had only limited success in breast cancer clinical trials.

Introduction

It has been over a century since Beatson demonstrated that oophorectomy was effective for treating advanced breast cancer. (1) Since then, endocrine therapies have become firmly established for managing all stages of breast cancer. In the last few years, many advances have been made in endocrine approaches to breast cancer therapy. Treatment choices have been refined and optimized by the development of assays for the presence of estrogen and progesterone receptors in tumors. Surgical techniques (i.e., oophorectomy, hypophysectomy, and adrenalectomy) have been largely replaced by a variety of pharmaceuticals (i.e., antiestrogens, LHRH agonists, aromatase inhibitors, androgens, estrogen, and progestins), and mechanisms, they often have similar objective response rates. Although endocrine therapies operate through different mechanisms, they often have similar objective response rates. Because breast cancer is a progressive disease and the development of drug resistance is common, endocrine therapies are given sequentially, with the least toxic therapy given first. In some cases, endocrine therapies have been almost entirely abandoned on the basis of toxicity. For example, diethyl-
stilbestrol was introduced in the 1940s as an endocrine therapy for postmenopausal advanced breast cancer (6). Because diethylstilbestrol was associated with side effects such as upper gastrointestinal distress, thromboembolic risk, fluid retention, stress incontinence, and withdrawal bleeding, it all but disappeared from the clinic after the introduction of tamoxifen in the 1970s. Likewise, androgens are associated with virilization, nausea, hepatotoxicity with cholestasis, increased libido, and hypercalcemia; as a consequence, they have been relegated to fourth-line therapy for advanced breast cancer in postmenopausal women.

Current and Future Directions in Endocrine Therapy

Nonsteroidal Antiestrogens

Tamoxifen. Tamoxifen (Fig. 3) is the first-line endocrine therapy for all stages of breast cancer. It was first approved by the FDA in 1977 for the treatment of advanced breast cancer in postmenopausal women and has since been approved for: (a) the treatment of advanced breast cancer in premenopausal women; (b) use with chemotherapy; (c) adjuvant monotherapy in postmenopausal women with node-positive breast cancer; (d) the treatment of node-negative breast cancer; and (e) male breast cancer.

In postmenopausal women with advanced breast cancer, tamoxifen induces objective responses in about one-third of unselected patients; a higher response rate is observed in women with ER-positive tumors (7). Adjuvant therapy with tamoxifen has reduced recurrence rates, mortality, and the incidence of contralateral breast cancer (8). The duration for which to give adjuvant tamoxifen therapy is an issue that remains to be resolved. It is clear that 5 years is better than 2 years, (9) but there are conflicting data as to whether longer than 5 years would be even better (or worse). The National Cancer Institute recommended limiting adjuvant tamoxifen to 5 years after the National Surgical Adjuvant Breast and Bowel Project B-14 trial revealed no additional benefit of longer therapy in patients with node-negative breast cancer (10). However, the Eastern Cooperative Oncology Group recently published preliminary results (11) of a trial showing prolonged disease-free survival with longer than 5 years compared with 5 years in women with ER-positive breast cancer.

Because tamoxifen was found to prevent new tumors from developing in the opposite breast, the drug is presently being studied in worldwide breast cancer prevention trials in healthy women at increased risk for the disease (12). The use of tamoxifen in healthy women has been controversial. Although tamoxifen is generally considered safer than alternative endocrine therapies such as androgens, estrogens, and progestins, it is not without toxicity. In addition to vasomotor and gynecological side-effects (e.g., hot flashes, vaginal discharge, and irregular menses) and an increase in the rate of thromboembolic events (1% in the B-14 trial; Ref. 10), the drug has been associated with a modest increase in the risk for endometrial cancer (2 cases per 1000 patients/year; Refs. 13 and 14). About 250 cases of tamoxifen-associated endometrial cancer have been reported since 1985 (15). It is not known what role tamoxifen plays in the etiology of these cancers (13); tamoxifen may act as a tumor initiator or promotor or may only enhance detection of preexisting endometrial cancer (detection bias). Because exposure to unopposed estrogen has been linked...
to endometrial cancer, the partial estrogenic activity of tamoxifen has been suspect. It is important to note that all of the nonsteroidal antiestrogens in clinical development exhibit some degree of estrogen agonist activity (2). These new agents will require vigorous long-term study before a conclusion can be reached regarding the risk of endometrial cancer.

Toremifene. Several new nonsteroidal antiestrogens have been developed, and one of these, toremifene, has been approved by the FDA for use in advanced breast cancer. In a comparative trial involving women with advanced breast cancer (16), toremifene (60 and 200 mg) showed similar efficacy and safety to tamoxifen (20 mg). The higher dose of toremifene had no benefit over the lower dose and was associated with an excess of liver function abnormalities; thus, 60 mg/day toremifene was approved for advanced breast cancer.

Toremifene is not yet indicated for adjuvant therapy, and long-term data are lacking on the agent. Therefore, it is not yet known whether toremifene will have any safety advantage compared with tamoxifen. However, it has been shown that toremifene, like tamoxifen, has a proliferative (estrogenic) effect on the uterus (17). The ultimate place of toremifene in therapy remains to be seen. Due to major cross-resistance between the two agents, it is unlikely that toremifene will be used as second-line therapy after tamoxifen (18, 19).

Droloxifene. Droloxifene (3-hydroxytamoxifen) is an antiestrogen in advanced clinical trials that shows higher binding affinity for the estrogen receptor than tamoxifen (20). In a multicenter Phase II trial involving postmenopausal women with advanced breast cancer (21), objective responses were seen in 30% of patients receiving 20 mg of droloxifene, compared with 47% of the 40-mg group and 44% of the 100-mg group. The median response durations were 12, 15, and 18 months, respectively. The most common side effects with droloxifene were hot flashes, lassitude, and nausea. Ongoing Phase III trials are comparing the safety and efficacy of droloxifene to tamoxifen. Interestingly, because droloxifene is eliminated from the body more rapidly than tamoxifen, it may have a role in combination chemohormonal therapy (6).

Raloxifene. Raloxifene is a benzothiophene antiestrogen that was being developed for breast cancer therapy but now is in clinical trials for the prevention and treatment of postmenopausal osteoporosis (22). In postmenopausal women, raloxifene (50 mg/day) was associated with significant reductions in total serum and low-density lipoprotein cholesterol as well as serum markers of bone turnover (i.e., osteocalcin and alkaline phosphatase; Ref. 23). If raloxifene becomes available for the prevention of osteoporosis in healthy postmenopausal women, a side benefit may be a reduction in the risk for breast cancer and coronary heart disease (3, 24).

Steroidal Antiestrogens

As discussed, the nonsteroidal antiestrogens all possess partial estrogenic activity. Steroidal antiestrogens have been developed that have no estrogenic activity and are thus less likely to have a proliferative effect on the endometrium. These compounds were derived from the estradiol molecule, in contrast to the nonsteroidal antiestrogens, which were derived from the triphenylethylene structure of tamoxifen. One steroidal antiestrogen, ICI 182,780 (Faslodex; Fig. 3), has entered clinical trials. In vitro, this agent has a high affinity for the estrogen receptor and high potency against ER-positive breast cancer cell lines (25). In a clinical trial (26), 56 postmenopausal women were randomized to ICI 182,780 (6 or 18 mg by injection) or no treatment for 7 days before primary breast surgery. ICI 182,780 significantly reduced expression of ER (P < 0.01), progesterone receptor (P < 0.05), and Ki67 (proliferation-associated nuclear antigen; P < 0.05) in ER-positive breast tumors. Expression of an estrogen-regulated protein (p52) was reduced, irrespective of tumor ER status.

In a Phase I trial (27), 19 patients with advanced breast cancer who had become resistant to tamoxifen received ICI 182,780 until progression (median, 25 months; Ref. 28). Thirteen patients responded to treatment (7 with a partial response and 6 with stable disease), indicating a lack of cross-resistance with tamoxifen. ICI 182,780 was well tolerated.

Although further clinical study of ICI 182,780 is necessary, potential advantages include a lack of proliferative effect on the endometrium and a lack of cross resistance with tamoxifen. If the efficacy and safety of ICI 182,780 are established in Phase III trials, this agent may have a role as second-line therapy after tamoxifen.

LHRH Agonists

In premenopausal women with advanced breast cancer, a desirable goal of endocrine therapy is to inhibit ovarian estrogen production.
production, which is under the control of circulating gonadotropins produced by the pituitary. Gonadotropin production is under the control of hypothalamic LHRH, which is normally released in a pulsatile fashion. Continuous treatment with LHRH agonists dramatically reduces levels of serum gonadotropins, and hence estradiol; in premenopausal women, this is essentially a medical (and reversible) form of castration (29). LHRH agonists may also have a direct cytotoxic effect on cancer cells (30).

Although a number of LHRH agonists have been evaluated for the treatment of breast cancer (e.g., goserelin, buserelin, leuprolide, and triptorelin), only goserelin acetate implant is indicated (FDA approved) for breast cancer in the United States. Objective response rates to LHRH agonists have ranged from 31–63% in premenopausal women with advanced breast cancer, similar to response rates seen with oophorectomy (30). As with other endocrine therapies, the frequency of response to LHRH agonists is higher in tumors that are hormone receptor positive. Side-effects with LHRH agonists consist of injection site reactions, tumor flare, and menopausal symptoms.

Recent results from the Early Breast Cancer Trialists’ Collaborative Group have contributed to a renewed interest in ovarian ablation as adjuvant therapy (8), and studies of the adjuvant use of LHRH agonists in premenopausal women are under way. In 1992, the Early Breast Cancer Trialists’ Collaborative Group published results of a 15-year follow-up on the effects of ovarian ablation (by surgery or radiation) on recurrence and death in women diagnosed with early breast cancer. For women <50 years of age at randomization ($n = 2102$), the recurrence-free survival rates were 58.5% versus 48.3% ($P = 0.0004$) for patients treated with ovarian ablation versus no therapy, respectively. The overall survival rates were 52.9 and 42.3%, respectively ($P = 0.00007$). The conclusion of this overview was that ovarian ablation was associated with an approximate 25% reduction in the annual odds of recurrence and death. In this same overview, investigators examined the survival and recurrence rates in patients treated with chemotherapy plus ovarian ablation versus chemotherapy alone. They found a 20% reduction in the annual odds of recurrence and death with combination therapy versus chemotherapy alone. It is surmised that LHRH agonists as adjuvant therapy in premenopausal women might offer similar results; this supposition awaits results of clinical trials.

### Aromatase Inhibitors

In postmenopausal women, the ovary has ceased functioning. However, estrogens are produced in peripheral tissues such as muscle, fat, and the breast tumor itself, from androgens secreted by the adrenal gland (Fig. 2). The final enzyme in this synthesis pathway for estrogens is aromatase. Inhibition of aromatase is an effective therapeutic strategy in postmenopausal women with advanced breast cancer.

### Nonselective Aromatase Inhibitors

**AG.** AG (Fig. 4) was the first widely used aromatase inhibitor for advanced breast cancer (31). AG is a nonselective aromatase inhibitor in that it inhibits other cytochrome P-450 enzymes, thereby inhibiting the synthesis of other steroid hormones (Fig. 5). As a consequence, therapy with AG usually requires supplemental corticosteroids. This regimen is associated with side effects such as skin rash, lethargy, and orthostatic hypotension. Therefore, although AG has shown comparable efficacy to tamoxifen, its side-effect profile has relegated this agent to third-line status (after tamoxifen and progestins). Also, the use of AG has rapidly decreased with the availability of newer aromatase inhibitors.

### Selective Aromatase Inhibitors

Newer aromatase inhibitors are more selective, have fewer side-effects, and do not require coadministration of corticosteroids (31, 32). This structurally diverse group of inhibitors includes androstenedione derivatives (formestane), imidazole derivatives (fadrozole), and triazole derivatives (anastrozole, letrozole, and vorozole; Fig. 4).

Aromatase inhibitors can be divided into two types: suicide inhibitors and competitive inhibitors (33). Suicide inhibitors are steroidal compounds that form an irreversible covalent bond with the aromatase enzyme, and thus have lasting effects in vivo. The continued presence of the drug to maintain inhibition is not necessary when using suicide inhibitors, and the chance of toxic side effects will, therefore, be reduced. Competitive inhibitors are mostly nonsteroidal and reversibly bind to the enzyme in competition with the natural substrate. Whether the different
mechanisms of interaction with aromatase results in clinical differences among these agents is yet to be determined.

**Formestane**. Formestane (4-hydroxyandrostenedione) is a selective suicide aromatase inhibitor indicated for advanced breast cancer in postmenopausal women (outside of the United States). In 136 unselected patients with advanced breast cancer, formestane (250 mg i.m. every 2 weeks) demonstrated a 26% response rate (34). In this study, 13% of patients had injection site reactions, and five patients experienced an anaphylactoid reaction after inadvertent i.v. administration. Although the high selectivity of formestane represents a major advance, the need for i.m. administration is an impediment to widespread acceptance of this agent in clinical practice.

**Anastrozole**. Anastrozole is a selective, nonsteroidal competitive aromatase inhibitor that was approved by the United States FDA in 1996 for the treatment of advanced breast cancer in postmenopausal women. After once-daily oral dosing of 1 mg in postmenopausal women, serum estradiol levels are suppressed to assay limits (35). Two Phase III multicenter trials have been conducted comparing double-blind anastrozole (1 and 10 mg/day) with open-label megestrol acetate (40 mg q.i.d.) for second-line treatment of advanced breast cancer in 764 postmenopausal women (36). About 40% of patients in each group benefited from therapy in terms of objective response or stable disease (37). There were no significant differences among the three treatments with respect to objective response rates or time to disease progression (median, 21 weeks). However, a recent update with longer follow-up has revealed a significant advantage in overall survival for the group receiving 1 mg/day anastrozole compared with megestrol (37). Patients treated with 1 mg of anastrozole had a 22% lower risk of death compared with megestrol acetate. Gastrointestinal disturbances were more common in patients receiving anastrozole compared with patients receiving megestrol acetate, although the difference was not significant. In contrast, megestrol acetate was associated with significant and progressive weight gain. Ongoing Phase III trials are comparing the safety and efficacy of anastrozole with tamoxifen for first-line use in the metastatic setting. In addition, anastrozole is being evaluated for use as an adjuvant treatment.

**Fadrozole**. Fadrozole (CGS 16949A) is a nonsteroidal, p.o. active, competitive aromatase inhibitor that has undergone extensive clinical testing in postmenopausal women with advanced breast cancer. It is not available in the United States, but it is available in Japan. Fadrozole exhibits greater potency and selectivity than AG (2, 38), but it is not entirely selective because it appears to interfere with adrenal steroidogenesis to some extent (39, 40).

Fadrozole (1 mg b.i.d.) was studied in two double-blind Phase III studies in which it was compared to megestrol acetate (40 mg q.i.d.) for second-line therapy of advanced breast cancer (38). A total of 683 postmenopausal women were enrolled. The combined overall response rates were 12.2% for fadrozole and 14.2% for megestrol acetate. No significant differences between treatments were seen in response rates, response durations, time to progression, or median survival. Fadrozole was associated with a higher incidence of nausea and vomiting, whereas patients treated with megestrol acetate were more likely to have experienced dyspnea, edema, and weight gain.

Fadrozole (1 mg b.i.d.) has also been compared with tamoxifen (20 mg/day) for first-line treatment of postmenopausal women with advanced breast cancer (41). A total of 212 women were enrolled. Prognostic factors were balanced between the two treatment groups, with the exception of an excess of visceral metastatic disease in the fadrozole group. Response rates were 20% for fadrozole and 27% for tamoxifen; time to treatment failure was 6.1 and 8.5 months, respectively. Fadrozole was better tolerated than tamoxifen [WHO grade 2 toxicity 13% versus 27% of patients, respectively (P = 0.009)].

**Letrozole**. Letrozole (CGS 20267) is a nonsteroidal competitive aromatase inhibitor that, like anastrozole, offers high selectivity and once-daily oral dosing (2). Recently, letrozole was approved for use as second-line treatment in postmenopausal women with advanced disease. Letrozole has been studied in two Phase III trials, one comparing letrozole to megestrol acetate, the other to aminoglutethimide. Both studies involved postmenopausal women with advanced breast cancer who had progressed on antiestrogen therapy. The first study (42) consisted of three treatment groups: 0.5 mg/day letrozole, 2.5 mg/day letrozole, and 160 mg/day megestrol acetate. Letrozole (2.5 mg) produced a significantly higher response rate (P = 0.047), with a trend toward a longer time to treatment failure than megestrol acetate. The 2.5-mg letrozole dose appeared to be significantly more effective than the 0.5-mg dose, although the degree of estrogen suppression was similar for the two
doses. Compared to letrozole, megestrol acetate was associated with a higher incidence of serious adverse events (primarily cardiovascular and thromboembolic events) and weight gain. The second study compared letrozole (0.5 and 2.5 mg/day) with AG (250 mg b.i.d.) and was performed with more rigorous criteria for response (43). Overall, the objective response rates for letrozole were lower (16.7 and 17.7% for 0.5 and 2.5 mg, respectively) than in the previous study, probably as a result of the more rigorous criteria used. The objective response rate for AG was 11.2% (no \( P \) given). However, letrozole was significantly better than AG in time to progression (risk ratio, 0.68; \( P < 0.004 \) for 2.5 mg of letrozole). More patients in the AG arm reported adverse events, and letrozole was well tolerated.

**Vorozole.** Vorozole is yet another selective nonsteroidal competitive aromatase inhibitor that is active when taken p.o. Two preliminary reports have appeared describing results from Phase III trials with vorozole (44, 45). In one of these, vorozole (2.5 mg/day) was compared with megestrol acetate (40 mg q.i.d.) in 452 postmenopausal women with advanced breast cancer who had failed on tamoxifen (45). In this open-label study, vorozole and megestrol acetate had comparable response rates (complete response + partial response, 10.5% versus 7.6%), with vorozole showing a nonsignificant trend toward a longer response duration (18.2 versus 12.5 months, \( P = 0.07 \)). Although both treatments were well tolerated, vorozole had a lower incidence of weight gain.

As a group, the selective, nonsteroidal aromatase inhibitors (anastrozole, fadrozole, letrozole, and vorozole) have similar efficacy to megestrol acetate, which had occupied the position of second-line therapy for metastatic disease in postmenopausal women. However, the new aromatase inhibitors have significantly better side-effect profiles, particularly with regard to weight gain. Thus, the selective, nonsteroidal aromatase inhibitors are replacing megestrol acetate for second-line use in this group of patients. This relationship is illustrated in Fig. 6 for anastrozole, the first member of this group of drugs to be approved in the United States.

Aromatase inhibitors are not indicated for premenopausal women because compensatory mechanisms can actually cause an increase in estrogen production by the ovaries. However, aromatase inhibitors may be valuable in premenopausal women who have progressed after oophorectomy (Fig. 6).

**Progestins**

Progestins have been used for treating metastatic breast cancer since the 1950s, although their mechanism of action remains uncertain. Currently, the only progestin indicated for postmenopausal advanced breast cancer in the United States is megestrol acetate. A second progestin, medroxyprogesterone acetate, is available outside the United States for breast cancer and worldwide in a depot form for contraceptive use. Both of these agents are synthetic, p.o. active derivatives of progesterone (46).

Overall response rates for megestrol acetate in metastatic disease are about 30% in unsellected patients (47). Although the efficacy of megestrol acetate appears to be similar to that of tamoxifen, the side-effect profile of this progestin has relegated it to second-line therapy. Weight gain is the most significant side-effect associated with progestin therapy and appears to be related to an increase in appetite rather than fluid retention. Although weight gain would be desirable in the subset of breast cancer patients with cachexia, it has a negative impact on body image for the majority of patients. Thromboembolism represents a serious side-effect of the progestins and may occur in 4–5% of patients.

**Antiprogestins**

Because progesterone (as well as estrogen) is believed to stimulate proliferation of breast epithelium, it has been hypothesized that antiprogesterone therapy would be effective in the treatment of breast cancer. Mifepristone (RU486) is the first clinically available antiprogestin. Currently available overseas as an abortifacient, the agent has undergone clinical study for the treatment of advanced breast cancer (48).

In a Phase II trial (49), mifepristone (200 mg/day) was administered to 28 women with previously untreated, progesterone-positive advanced breast cancer. Three patients had a partial response for an overall response rate of 10.7%. Toxicity was mild to moderate, consisting primarily of nausea, lethargy,
anorexia, and hot flashes. The investigators concluded that the efficacy of mifepristone was minimal, despite an optimal patient population.

A second antiprogestin, onapristone, has undergone early clinical evaluation, but its development was discontinued due to liver toxicity (2).

Both mifepristone and onapristone are nonselective antiprogestins; they also bind to glucocorticoid and androgen receptors. New antiprogestins are in development that are more potent and more selective for the progesterone receptor (50).

**Antiandrogens**

Because androgen receptors are present in 30–50% of primary breast cancers (51), there has been interest in studying the use of antiandrogens for this disease.

Flutamide, a pure nonsteroidal antiandrogen used in the treatment of prostate cancer, has been evaluated in Phase II clinical trials for metastatic breast cancer. In one such trial (52), only one response lasting 8 weeks was observed in 29 evaluable patients, leading the investigators to discontinue further evaluation of flutamide for breast cancer.

A study of metastatic breast cancer in males found that the combination of an antiandrogen (cyproterone acetate) with an LHRH antagonist (buserelin) induced objective responses in 7 of 11 patients (53). The side-effects of this treatment were loss of libido, impotence, and hot flashes. Further studies are needed to define the role of antiandrogens and combinations of antiandrogens with LHRH antagonists in male breast cancer.

**Discussion**

In the last 5 years, a variety of new endocrine agents have entered advanced clinical trials, and three of these, anastrozole, toremifene, and letrozole, have received marketing approval in the United States. Two classes of endocrine agents are the focus of much of the research: the antiestrogens and the aromatase inhibitors.

Because tamoxifen has been so successful in the adjuvant breast cancer setting, the search is on for new antiestrogens that bind ER with higher affinity and show reduced estrogenic activity in the endometrium. A new type of steroidal antiestrogen has been developed that is completely devoid of estrogen agonist activity and lacks cross-reactivity with tamoxifen. The ultimate clinical role of this new therapy awaits the results of Phase III trials.

Because long-term estrogen deprivation in postmenopausal women can contribute to osteoporosis and cardiovascular disease, the use of agents such as steroidal antiestrogens presents an important dilemma. Without the estrogen-agonist protective effects on bones and lipids (e.g., as offered by the nonsteroidal antiestrogen tamoxifen), if these agents are to be used as adjuvant therapies, other agents to prevent osteoporosis and cardiovascular events may also have to be administered concomitantly.

The development of selective nonsteroidal aromatase inhibitors that can maximally suppress estrogen levels and are formulated for once-daily oral dosing is another advance in endocrine therapy for breast cancer. Because they have fewer side-effects than the progestins, selective aromatase inhibitors are expected to replace progestins as second-line therapy after tamoxifen. Whether the new selective aromatase inhibitors will have a role in the adjuvant setting remains to be tested in clinical trials. One rationale for using aromatase inhibitors as adjuvant therapy is their good tolerability profile in combination with efficacy rates comparable with other endocrine therapies for treatment of postmenopausal advanced breast cancer; again, the possible effects of long-term estrogen deprivation in aggravating osteoporosis and cardiovascular disease would need to be taken into account.

The hope is that the newer endocrine therapies discussed in this report will offer clinicians the ability to treat patients with hormone-responsive breast cancer better (i.e., with less toxicity).

**References**


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