Effects of the New Selective Estrogen Receptor Modulator LY353381.HCl (Arzoxifene) on Human Endometrial Cancer Growth in Athymic Mice

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ABSTRACT

Purpose: Arzoxifene (Arzox) is a novel benzothiophene analogue with selective estrogen receptor modulator activity similar to raloxifene. Arzox is being developed as a treatment for breast cancer and has a predominantly antiestrogenic effect on the rodent uterus. Our objectives were to verify whether the novel selective estrogen receptor modulator, Arzox, can be a good first-line agent and also be effective at controlling the growth of endometrial cancer after exposure to tamoxifen (Tam).

Experimental Design: We compared the effects of Tam and Arzox on the growth of estrogen responsive ECC-1 endometrial cancer cells in vitro, and we determined their antitumor effects on ECC-1 and EnCa101 endometrial carcinoma growth in athymic mice.

Results: We observed that estrogen receptor protein expression is down-regulated by Arzox to the same extent as raloxifene, whereas 4-hydroxytamoxifen, the active metabolite of Tam, does not affect estrogen receptor protein levels. Tam and Arzox inhibit the growth of Tam-naive ECC-1 tumors in athymic mice. However when Tam-stimulated or estrogen-stimulated (which had been treated with Tam previously) EnCa101 endometrial tumors were treated with Tam or Arzox, we observed a stimulatory effect of both compounds in these models.

Conclusions: The results indicate that Arzox may be a good first-line agent, but it may be ineffective at controlling the growth of endometrial cancer after exposure to Tam. Our data suggest that Arzox stimulates endometrial tumor growth to at least the same extent as Tam, thereby suggesting a limited role as a second-line agent for the patient on Tam who develops occult endometrial cancer.

INTRODUCTION

Endometrial carcinoma is the most common malignancy of the female genital tract, and it is estimated to account for approximately 36,100 new cases and more than 6,500 deaths in 2000 in the United States (1). Several risk factors for the development of endometrial carcinoma are related to an extended exposure to unopposed estrogen action, such as in nulliparity, late menopause, obesity, diabetes mellitus, estrogen replacement therapy, and Tam treatment. Tam has a low incidence of serious side effects, however, it has a partial estrogen agonist effect in the human uterus (2). The National Surgical Adjuvant Breast and Bowel Project-P1 study showed that Tam does not increase the risk of endometrial cancer in premenopausal women, but it does increase the risk by 3- to 4-fold in postmenopausal women (3). It is important to stress, however, that the stage and grade of endometrial cancers observed in postmenopausal women were the same as in the general population (4).

The mechanism of uterine carcinogenesis caused by Tam is unknown. Two possible mechanisms have been proposed: (a) conversion of the drug to electrophilic metabolites that damage cellular DNA; and (b) an estrogen-agonist action on the uterus, promoting endogenous lesions. In vitro studies with human tissues or cells do not show significant DNA adduct formation by Tam in endometrium. However, in vivo studies have demonstrated contradictory results with DNA adduct formation in human endometrium (5). It seems most likely that, in women treated with Tam, the increased incidence of endometrial cancer is related to its estrogenic effects promoting uterine cell proliferation and stimulating the growth of preexisting endometrial cancers, because 5 years is not enough time to complete the carcinogenic process (6). In addition, women with both previous estrogen replacement therapy exposure and higher body mass

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4 The abbreviations used are: Tam, tamoxifen; ER, estrogen receptor; Arzox, arzoxifene; Ral, raloxifene; SERM, selective estrogen receptor modulator; E2, 17β-estradiol; 4-OHT, 4-hydroxytamoxifen.
index have the highest risk of Tam-associated endometrial cancer (6).

Tam (Fig. 1) is the endocrine adjuvant treatment of choice for all ER-positive breast cancers (7). Not surprisingly, long-term adjuvant Tam treatment does not control the recurrence of all ER-positive breast cancers, and drug resistance can develop (8). In fact, some of these tumors seem to be stimulated by Tam (9, 10). Several molecular and cellular mechanisms have been proposed as contributors to the acquisition of this resistant phenotype (11, 12), including the selection of ER mutants, alterations in the intracellular pharmacology and metabolism, ligand-independent ER-mediated transcription, and perturbation of the interaction of ER with corepressors of transcription. However, most of these Tam-stimulated tumors retain expression of the ER (13) and respond to a second-line endocrine therapy (14). In addition to this problem, concerns about the uterine safety of Tam (3, 4) have naturally provoked a search for a viable agent for first- or second-line breast cancer in patients who develop occult endometrial cancer.

Arzox is a new benzothiophene analogue that is structurally related to Ral (Fig. 1). Like Ral, Arzox is classified as a SERM, based on its differential estrogenic/antiestrogenic effects in vivo on estrogen-target tissues (15). Arzox was designed to improve the bioavailability of Ral and provide sustained antiestrogenic blockade in the treatment of breast cancer. A preliminary clinical study of Arzox shows modest activity as a treatment for ER-positive metastatic breast cancer in postmenopausal women (16). As Tam is used ubiquitously as an adjuvant in breast cancer treatment (7), any new SERM will almost certainly be used after the failure of adjuvant Tam therapy. In an earlier publication, we have reported that Arzox is effective as an antitumor agent in one model of Tam-stimulated breast cancer (T47D) but is cross-resistant in another (MCF-7) (17).

We now address the issue of Arzox and the growth of human endometrial carcinoma. The association between occult endometrial cancer and breast cancer is well known (18–20). If this paradigm is correct, then it is essential to evaluate the potential endometrial safety of a new SERM in the laboratory. We have used several different laboratory models of endometrial cancer to represent the application of Arzox treatment in the clinic. (a) endometrial cancer (ECC-1) never exposed to Tam; (b) an endometrial cancer initially exposed to chronic Tam treatment but passaged in E2-treated athymic mice for 3 years (EnCa101-E2); and (c) EnCa101-Tam endometrial carcinoma, which is stimulated by Tam. These models represent: (a) patients never treated with Tam; (b) patients previously treated with Tam and now requiring a second-line endocrine therapy years after adjuvant Tam was stopped; and (c) patients treated with a second-line agent. Using our unique models of human endometrial carcinoma, we determine whether Arzox would be a viable agent for first- or second-line breast cancer in patients who develop occult endometrial cancer.

MATERIALS AND METHODS

The ECC-1 human endometrial cancer cell line was derived from a primary well-differentiated, ER-positive endometrial adenocarcinoma (21). ECC-1 cells were maintained in flasks with phenol red containing DMEM supplemented with 10% fetal bovine serum and 1% L-glutamine, 1% nonessential amino acids, 100 units/ml penicillin, and 100 mg/ml streptomycin. Before experiments, cells were maintained in phenol red-free DMEM with stripped fetal serum with the addition of 1% L-glutamine, 1% nonessential amino acids, 100 unit/ml penicillin, and 100 mg/ml streptomycin for at least 4 days. Cells were grown at 37°C in a humidified 5% CO2 atmosphere.

Growth Assay. The ECC-1 cells were harvested after trypsinization and seeded into each well of 24-well plates at a concentration of 1.5 × 104 cells (in 1 ml of estrogen-free media). The growth assay was performed as described previously (22), with doses of compounds ranging from 10−10 to 10−6 M. After 5 days of treatment, media was aspirated, 1 ml of 0.1× solution of hypotonic calcium, magnesium-free Hanks’ balanced saline solution was added to each well, and cells were chilled at 4°C for 10 min. The cells were sonicated, and 100 μl of the sonicated cell solution was transferred to an assay tube. A standard DNA curve was completed using a stock concentration of DNA (20 μg of calf thymus DNA/ml in hypotonic calcium, magnesium-free Hank’s balanced saline solution with 0.2 mg/ml BSA). The cell solution was incubated for at least 1 h in 1.5 ml of 1:200 solution of Hoechst dye (Polysciences, Inc.) and PES (2 mM NaCl, 50 mM Na2HPO4, and 1 mM EDTA [pH 7.4]) per assay tube. DNA concentrations were measured using a fluorometer. The activation wavelength was 356 nm, and the wavelength setting for reading samples was 458 nm.

Western Blot Analysis. Western blotting was performed as described previously (23). The ECC-1 medium was replaced with fresh estrogen-free media containing E2 (10−6 M), 4-OHT (10−7 M), Ral (10−7 M), Arzox (10−7 M), ICI182,780 (10−7 M), or ethanol (control). The ECC-1 cells exposed to different compounds were harvested after 24 h treatment by scraping with a rubber policeman, in a PBS/EDTA solution. The cells were then pelleted by centrifugation, and the cell pellet was resus-
implanted s.c. and replaced every 8 weeks. The 0.3 cm E2 (Sigma Chemical Co.) made as described previously (27) were suspended in protein extraction buffer [0.5% NP40, 2% glycerol, 1 mM DTT, 1 mM EDTA, 150 mM NaCl, 50 mM Tris (pH 7.4), 1 mM EGTA, 3 mM phenylmethanesulfonyl fluoride, 25 μg/ml leupeptin, 9 μg/ml aprotinin, 25 μg/ml trypsin inhibitor, and 25 μg/ml t-chymotrypsin]. Protein concentration from supernatant was measured using the Bio-Rad Protein Assay kit, and equal amounts of protein were run according to a standard Western blot protocol. The ER primary antibody used was AER311 (Neomarkers, Fremont, CA), and β-actin antibody AC-15 (Sigma Chemical Co., St. Louis, MO) was used to standardize loading. The appropriate secondary antibody conjugated with a horseradish peroxidase kit (Amersham Corp., Arlington Heights, IL) was used to visualize bands using an enhanced chemiluminescence visualization kit (Amersham Corp., Arlington Heights, IL). The membrane was exposed to Kodak X-Omat film for 10 s.

**Athymic Mouse Model.** The ECC-1 endometrial tumor was developed from 10 million ECC-1 cells injected bilaterally into mammary fat pads of ovariectomized athymic mice 4–5 weeks of age (Harlan Sprague Dawley, Madison, WI). E2 was administered via a 1 cm silastic capsule implanted s.c., which stimulated tumor growth (24). When ECC-1 tumors reached 1.0 cm², a single tumor was harvested, and 1-mm³ tumor pieces were bitransplanted into the anterior axillary region of 30 athymic mice, which were treated as follows: 0.3 cm E2 capsules (eight mice); 1.5 mg of Arzox (eight mice); 1.5 mg of Arzox + 0.3 cm E2 capsules (eight mice); or control (six mice). We also retransplanted ECC-1 tumors into 40 athymic mice divided into four groups of 10 and treated with 0.3 cm E2 capsules, 0.5 mg of Tam, 0.5 mg of Tam + 0.3 cm E2 capsules, or control. The EnCa101-Tam endometrial tumors used in these experiments were developed in 1984 (25). EnCa101-E2 tumors were developed by passing EnCa101-Tam tumors in mice treated with E2 for 3 years (26). EnCa101-E2 endometrial tumors were transplanted into 60 athymic mice divided into six groups of 10 and treated with 0.5 mg of Tam, 0.5 mg of Tam + 0.3 cm E2 capsules, 1.5 mg of Arzox, 1.5 mg of Arzox + 0.3 cm E2 capsules, 0.3 cm E2 capsules, or control. EnCa101-Tam endometrial tumors were transplanted into 40 athymic mice and divided into four groups of 10 then treated with 0.3 cm E2 capsules, 0.5 mg of Tam, 1.5 mg of Arzox, or control. Tumor measurements were performed weekly using Vernier calipers. The cross-sectional area was calculated using the formula: length × width/4 × π. The Animal Care and Use Committee of Northwestern University, Chicago, IL, approved all procedures involving animals.

**Hormone and Drug Treatments.** Silastic E2 capsules (Sigma Chemical Co.) made as described previously (27) were implanted s.c. and replaced every 8 weeks. The 0.3 cm E2 capsules produced a mean 83.8 pg/ml of serum E2, whereas 1.0 cm E2 capsules produced a mean 379.5 pg/ml of serum E2 (26). Tam (Sigma Chemical Co., St. Louis, MO) or Arzox (generous gifts of Eli Lilly, Indianapolis, IN) were first dissolved in ethanol and suspended in a solution of 90% carboxymethylcellulose (1% carboxymethylcellulose in double-distilled water) and 10% polyethylene glycol 400/Tween 80 (99.5% polyethylene glycol 400 and 0.5% Tween 80). Ethanol was evaporated under nitrogen before use. Tam or Arzox was administered by gavage at 0.5 or 1.5 mg, respectively, per mouse per day, 5 days/week.

**Statistical Analysis.** Comparisons in mean tumor between the animal groups were analyzed by ANOVA at each week and then an unpaired Student’s t test. The two-tailed P of the last week of each experiment was reported using StatMost 2.5 (Datamost Corp., Salt Lake City, UT).

**RESULTS**

To examine the antiestrogenic activity of Arzox on endometrial cell proliferation in vitro, we used ER-positive ECC-1 endometrial cancer cells (Fig. 2), which are extremely sensitive to the stimulatory effects of E2: at physiological concentration \((10^{-9} \text{ M})\), there was a 6-fold increase in DNA levels compared with control \((P < 0.001)\). In contrast, 4-OHT and Arzox did not stimulate ECC-1 cell proliferation compared with control at concentrations of \(10^{-9}–10^{-8} \text{ M}\). However, at low concentration \((10^{-10} \text{ M})\), 4-OHT and Arzox slightly increased the growth of ECC-1 cells (1-fold). We also demonstrated that 4-OHT and Arzox inhibited the proliferation of E2-stimulated \((10^{-9} \text{ M})\) ECC-1 cells in a dose-dependent manner. In addition, Arzox seems more efficient than 4-OHT in blocking E2-stimulated growth of ECC-1 in vitro \((EC_{50} \text{ Arzox}, 2.4 \times 10^{-9} \text{ M}; EC_{50} \text{ 4-OHT}, 2.93 \times 10^{-9} \text{ M})\).
proliferative effects of E2 than 4-OHT at lower concentrations (EC50 Arzox, 2.4 × 10−9 M; EC50 4-OHT, 2.93 × 10−8 M).

To characterize further the antiestrogenic activity of Arzox, we determined the effect on ERα protein levels in ECC-1 cells. It has been reported previously that estrogen decreases the transcription of ERα mRNA and protein levels in ECC-1 cells (22). Interestingly, 4-OHT slightly increases ERα expression in ECC-1 cells, but only at the protein level (22). It is widely accepted that the pure antiestrogen ICI182,780 destroys ERα protein (28). Ral decreases ERα expression in ECC-1 cells but not as profoundly as E2 (Fig. 3). Because Arzox is a benzothiophene-like compound structurally similar to Ral, we examined the effects of Arzox on ERα protein levels to confirm its similarity with Ral. In Fig. 3, Western blot analysis shows ERα protein levels in ECC-1 cells after treatment with E2, 4-OHT, Ral, Arzox, and ICI182,780. Arzox decreased ERα protein levels similarly to Ral but to a lesser extent than ICI182,780 (P < 0.01). These experiments were repeated three times.

Studies in vivo demonstrated the antiestrogenic action of Arzox. E2 maximally stimulated the growth of ECC-1 tumors transplanted into athymic mice (Fig. 4A). After 14 weeks of treatment, E2-stimulated growth was significantly greater than all other treatments (P < 0.001). In contrast, the 1.5 mg Arzox, or 1.5 mg Arzox + 0.3 cm capsule E2-treated groups did not grow after 14 weeks and were similar in size to the control group. Mice were then implanted with 1.0 cm E2 capsules after Arzox was stopped to determine whether the ECC-1 cells remained viable. E2 significantly stimulated tumor growth compared with the control group (P = 0.01), and the mean tumor size of was ~0.55 cm2 at 27 weeks. In the next experiment, we repeated this study with the ECC-1-transplanted tumors using Tam treatment (Fig. 4B). Tam produced similar results when compared with the previous experiment using Arzox (Fig. 4A). E2 stimulated tumor growth significantly more than the other groups (P < 0.001). Tam did not exhibit agonist properties compared with control, and Tam completely blocked the effects of postmenopausal E2.
However, when the mice were treated with 0.3 cm E2 capsules, there was no significant difference in tumor growth rates with either treatment (Fig. 5).

In Fig. 6, E2 and Tam stimulated EnCa101-Tam tumors to the same extent as 0.5 mg Tam (data not shown), and the combination of SERM with E2 stimulated tumor growth significantly more than control (Tam versus control, P = 0.001; Arzox versus control, P = 0.001). But there was no significant difference between the two antiestrogens.

The low dose of Arzox (0.5 mg) also stimulated the growth of EnCa101-Tam endometrial tumors to the same extent as 0.5 mg of Tam and 1.5 mg of Arzox (data not shown). Interestingly, both the 0.5 mg Tam and 1.5 mg Arzox treatments stimulated tumor growth compared with control (P < 0.005), but there was no difference in tumor growth rates with either treatment (Fig. 5).

However, when the mice were treated with 0.3 cm E2 capsules in addition to Tam and Arzox compounds, the tumors grew faster than with either antiestrogen alone (P = 0.034; 0.5 mg of Tam versus E2; P = 0.063; 1.5 mg of Arzox versus Arzox + E2). Tam and Arzox (at both doses) have similar agonist properties in EnCa101-E2, and both antiestrogens partially block the effects of E2 (P < 0.001 compared with E2), but there is no difference between the two antiestrogens. These results demonstrate that Arzox (at both doses) is cross-resistant with Tam in this tumor model.

EnCa101-Tam endometrial tumors grow with either E2 and Tam (26). In Fig. 6, E2 and Tam stimulated EnCa101-Tam growth, but there was no significant difference between the groups. By 9 weeks, the 1.5 mg-Arzox tumors had grown to a greater extent (P = 0.023) extent than the 0.5 mg Tam group (Fig. 6).

In addition to Tam and Arzox compounds, the tumors grew faster than with either antiestrogen alone (P = 0.034; 0.5 mg of Tam versus E2; P = 0.063; 1.5 mg of Arzox versus Arzox + E2). Tam and Arzox (at both doses) have similar agonist properties in EnCa101-E2, and both antiestrogens partially block the effects of E2 (P < 0.001 compared with E2), but there is no difference between the two antiestrogens. These results demonstrate that Arzox (at both doses) is cross-resistant with Tam in this tumor model.

DISCUSSION

Tam increases the incidence of endometrial carcinoma in postmenopausal patients (4), possibly because it acts as a partial estrogen agonist. However, Ral seems to be less estrogenic than Tam on the rodent uterus (29), and Ral does not increase human endometrial thickness (30). No increase in the incidence of endometrial cancer has yet been reported with Ral (31). The incidence of endometrial cancer in the postmenopausal population is low (~1/1000 women/year), so large study populations are required to obtain accurate estimates of increased risk for any new SERM. The increased incidence of human endometrial cancer with Tam treatment (32) was predicted in the laboratory with the EnCa101 endometrial cancer model (33). We believe this model has the potential to provide valuable information about Ral derivative, Arzox, and endometrial cancer risk.

Recently we reported that Ral (0.5 mg/day or 1.5 mg/day p.o.), stimulates the growth of Tam-stimulated MCF-7 breast tumors and EnCa101-Tam endometrial tumors in vivo (34). These results suggest that if Ral is used for osteoporosis prevention after 5 years of Tam, it could result in the growth of occult breast or endometrial cancers. Additionally, Ral seems to be cross-resistant with Tam in our short-term Tam-resistant breast cancer model (34), supporting the clinical finding that it is not of value in the treatment of advanced Tam-refractory breast cancer (35). Previously, we have also observed that Arzox is cross-resistant with Tam in MCF-7-Tam breast tumors, and Arzox can only partially block estrogen-stimulated growth of T47D breast tumors in athymic mice (17).

Although Ral is used to prevent and treat osteoporosis (30), it has only 2% bioavailability (36), which compromises the proposed use of Ral as a breast cancer treatment. Arzox is a SERM designed to have an extended bioavailability compared with Ral (15) and is currently being developed for breast cancer treatment (37). Arzox is less estrogenic than Tam on rodent uteri.
uterus (15). Because Arzox may be used in early-stage breast cancer, it is important to evaluate potential uterine side effects and document the effects on endometrial cancer growth in the laboratory to predict the likelihood of Arzox-associated endometrial cancers. We have used three model systems of endometrial cancer in vivo to simulate clinical applications with Arzox: (a) patients with breast cancer who have never been treated with Tam; (b) patients with breast cancer who have been treated with Tam previously; and (c) patients who have failed first-line Tam and have subsequently been switched to a second-line SERM (Arzox).

We found that in cell culture and in the Tam-naïve ECC-1 transplanted human tumor model, Arzox is effective as an antiestrogenic/antitumor agent. Arzox completely antagonized estrogen-stimulated growth in vitro and in vivo. Additionally, Arzox does not completely decrease ER protein levels and is similar to Ral in endometrial cancer cells. IC1182,780 causes destruction of ER (28) and, therefore, has an optimal action with low intrinsic activity of the ER complex and receptor loss to prevent endometrial cancer growth (26). Recently, we have demonstrated that IC1182,780 given twice a week s.c. (10 mg) has an optimal antitumor effect on the growth of T47D-Tam, MT2-Tam, MCF-7 breast cancers, and EnCa101-Tam endometrial cancer (38). The studies of IC1182,780 showing the activation of AP-1 in vitro (39) are an artifact that does not translate to therapeutic cross-resistance. The complete degradation of ER protein is only observed with the pure antiestrogen, whereas SERMs produce different responses. For example, 4-OHT slightly increases ER protein in ECC-1 endometrial cells, whereas Ral and Arzox decrease ER levels (Fig. 3). In an earlier study, we demonstrated that the reduction in ER expression with Ral and IC1182,780 does not result from a decrease in ER mRNA transcription (22).

Neither Tam nor Arzox stimulated ECC-1 tumor growth in vivo. This suggests that Arzox would be safe on the uterus in the treatment of endocrine therapy-naïve, postmenopausal patients. It is not surprising that Tam did not stimulate the growth of ECC-1 tumors in vivo, because the drug is showing promise as a hormonal therapy for advanced endometrial cancer (40). Similarly, there is a multicenter, Phase II study showing the efficacy and safety of Arzox (20 mg p.o/day) in advanced or recurrent progestogen-sensitive endometrial cancer (41).

Although Arzox is less estrogen-like than Tam in the rodent uterus (15), we have demonstrated that Arzox is cross-resistant with Tam in the EnCa101-Tam tumor model. These data suggest that special care must be taken when monitoring the uterine effects of Arzox in patients who recently have received Tam treatment. Additionally, Arzox is equivalent to Tam in stimulating the growth of an EnCa101 tumor that has been exposed previously to Tam (EnCa101-E2 tumors). Clearly, once the Tam-stimulated phenotype has been established, sometime in the natural history of a tumor, any SERM, e.g., Ral or Arzox, may stimulate growth. On the basis of our present and previous studies with Ral and toremifene (34), (26), we believe SERMs cannot inhibit the growth of endometrial cancers that are stimulated by Tam, but only the pure antiestrogen IC1182,780 (38), which destroys the ER, is able to inhibit such tumors. So, in terms of the endometrium, the pure antiestrogen seems to be the best option as a second-line hormonal therapy after Tam failure in breast cancer patients. The mechanism of SERM-stimulated growth pathway in endometrium is not clear, but a recent report (42) demonstrates that Arzox, E2, and Tam can activate uterine insulin-like growth factor I signaling pathways.

In summary, we suggest that the antiestrogenic actions of Arzox on the uterus may translate to clinical practice with the control of occult endometrial cancer growth in patients never exposed to Tam. In contrast, patients who have been exposed to Tam may remain at risk for endometrial cancer during Arzox treatment.

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