Preliminary Experience with Pure Antiestrogens

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Abstract

Endocrine therapy plays an important role in the management of all stages of breast cancer, and the development of effective endocrine therapies has focused on modifying the response of hormone-sensitive tumors to estrogen. The most widely used agents are the nonsteroidal antiestrogens or selective estrogen receptor (ER) modulators, the class to which tamoxifen, the standard in terms of antiestrogen therapy, belongs. Tamoxifen is effective in both adjuvant and first-line settings and is now used as prophylactic therapy in high-risk individuals. However, the partial agonist activity of tamoxifen on the uterus, coupled with "tumor flare" and the development of tamoxifen resistance, has limited its therapeutic utility. Attempts to eliminate the partial agonist activity of tamoxifen and increase its potency have led to the development of fulvestrant (Faslodex), the first in a new class of pure antiestrogens, the ER down-regulators. Fulvestrant has a high affinity for the ER compared with tamoxifen but has none of the agonist activities of tamoxifen. This new agent is showing promising clinical activity in the treatment of advanced breast cancer after tamoxifen therapy. Fulvestrant's lack of ER agonist activity may provide a longer duration of response compared with tamoxifen, as it did in a preclinical setting. Fulvestrant has demonstrated that it is at least as effective as the third-generation aromatase inhibitor anastrozole in patients whose disease has relapsed or occurred on prior endocrine therapy and is currently being evaluated in Phase III trials versus tamoxifen for the first-line therapy of advanced breast cancer. Future clinical studies will evaluate fulvestrant in adjuvant and neoadjuvant settings, together with its optimal sequencing in relation to tamoxifen and other endocrine therapies.

Introduction

Antiestrogen therapy, and tamoxifen in particular, has improved the treatment of all stages of breast cancer over the last 3 decades (1). The term "antiestrogen" encompasses all agents that antagonize the physiological effects of the female hormone estrogen or 17β-estradiol. Tamoxifen (Nolvadex), a nonsteroidal, triphenylethylene-based antiestrogen (Fig. 1) with tissue-specific estrogenic (agonist) and antiestrogenic (antagonist) activity, has been the antiestrogen of choice in the clinic for over 25 years. The biological effects of tamoxifen are mediated primarily by inhibiting the actions of estrogen mediated through its binding to the ER. The antiestrogenic activity of tamoxifen in the breast has established it as the standard for the treatment of all stages of breast cancer. Tamoxifen given for different durations in an adjuvant setting has been associated with an up to 47% reduction in the risk of contralateral breast cancer (2) and a 45% reduction in invasive cancer in patients with ductal carcinoma in situ (3). Furthermore, the prospective evaluation of tamoxifen for the prevention of cancer in high-risk women in the National Surgical Adjuvant Breast and Bowel Project P1 breast cancer prevention study (4) showed tamoxifen to reduce the relative risk of invasive cancer by 49% in all age groups. Although these observations have not been confirmed in two European studies, tamoxifen has been approved by the Food and Drug Administration for breast cancer prevention in high-risk individuals (5).

Long-term tamoxifen treatment is associated with at least two other clinical benefits normally associated with endogenous systemic estrogen. These are the maintenance of bone density (6, 7) and the lowering of circulating low-density lipoprotein cholesterol (8) with a beneficial effect on cardiovascular disease (5, 9), both issues of importance to perimenopausal and postmenopausal women. However, tamoxifen is also associated with a slight increase in the risk of endometrial cancer (4, 9, 10) and as yet unsubstantiated concerns over second malignancies (11). These observations are of particular concern when tamoxifen is used in an adjuvant setting because patients may be receiving therapy for up to 5 years. Tamoxifen is also associated with a tumor-stimulatory effect, sometimes seen as a transient flare at the start of treatment (12), and perhaps most importantly with the acquisition of "tamoxifen resistance," in which tamoxifen no longer inhibits tumor growth and, in some cases, actually promotes it (13). Antiestrogen therapy is also associated with an increased incidence of thromboembolic phenomena, including deep-vein thrombosis, pulmonary embolism, and possibly cerebrovascular events (14, 15). The most common serious adverse event with tamoxifen is thromboembolism (4). However, despite these negative aspects of tamoxifen therapy, the benefits for the treatment and prevention of breast cancer are considered to substantially outweigh the risks.

Furthermore, the success of tamoxifen in the treatment of breast cancer has proved invaluable in the search for and development of new antiestrogens that selectively retain the favorable estrogenic and antiestrogenic properties of tamoxifen. In fact, it is the standard against which all new endocrine therapies, in-

1 Presented at the First International Conference on Recent Advances and Future Directions in Endocrine Therapy for Breast Cancer, June 21–23, 2001, Cambridge, MA.
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3 The abbreviations used are: ER, estrogen receptor; SERM, selective estrogen receptor modulator; ERD, ER down-regulator; PgR, progesterone receptor; ERE, estrogen response element; ROW, Rest of the World.
Fulvestrant: Mode of Action

New Antiestrogens

The last decade has seen an upsurge in the activity invested in the search for the successor to tamoxifen. The strategies used have included the chemical modification of tamoxifen, either by altering the side chains to produce new tamoxifen analogues such as toremifene (Ref. 16; Fig. 1), idoxifene (17), droloxifene (18), and TAT-59 (19, 20) or by altering the nonsteroidal triphenylethylene ring structure of tamoxifen to produce new nonsteroidal ring structures such as the benzothiophene derivative raloxifene (Fig. 1) and (21, 22) or the benzopyran derivative EM-800 (23). These nonsteroidal antiestrogens have all been classified as SERMs and exhibit mixed tissue-dependent agonist/antagonist activity. None of these nonsteroidal antiestrogens have yet shown any significant advantage over tamoxifen in clinical trials in terms of either efficacy or tolerance (24). Also, the possibility of cross-resistance between most of these agents and tamoxifen may limit their potential usefulness in the treatment of advanced disease after adjuvant tamoxifen therapy (24). Indeed, all of the triphenylethylene tamoxifen analogues, with the exception of toremifene (Fig. 1), have been withdrawn from development for the treatment of breast cancer.

Another avenue has been to produce steroidal analogues of estrogen with a bulky side chain at either the 7α (25–28) or 11β position of estradiol (29), which are completely lacking in agonist activity. These agents have been termed "pure" antiestrogens and include ICI 164,384, fulvestrant (Faslodex; formerly ICI 182,780), and RU 58668. The most advanced of these in terms of both preclinical and clinical evaluation is the steroidal compound fulvestrant (Fig. 1; Ref. 28).

Fulvestrant: Mode of Action

Fulvestrant is one of two steroidal antiestrogens with pure antiestrogenic activity developed from a series of 7α-alkyl analogues of estradiol (28). ICI 164,384 has been studied extensively in a preclinical setting, but it is the more potent fulvestrant that is being actively studied in clinical trials in patients with breast cancer (25, 26).

Fulvestrant is distinguishable from tamoxifen and the other SERMs, both pharmacologically and in terms of its molecular activity. Although both classes of agent mediate their effects through the ER, they differ significantly in their downstream effects (Table 2). Binding of estradiol and the nonsteroidal antiestrogens (SERMs) to the estrogen binding sites of the ER initiates a series of events, which include dissociation of heat shock proteins and ER dimerization. The dimerization process facilitates the binding of the ER to specific DNA EREs in the vicinity of estrogen-regulated genes (30, 31). In addition, many proteins interact with the receptor to act as corepressors or coactivators; to further complicate matters, at least 50 transcriptional activating factors modulate the effects of estrogen on the target gene (32, 33). There are also known to be at least two ERs, ER-α and ER-β (34–36), which have different tissue distributions. Both ERs contain two activating functions, AF-1 and AF-2, both of which are active when estrogen binds to the receptors. Neither activating function is active when the benzothiophene derivative raloxifene binds to the ER, and only AF-2 is inactive when tamoxifen binds to the ER. The latter scenario leads to incomplete attenuation of transcription, with the AF-1 domain allowing selective gene expression to occur. Thus, the partial agonist activity of tamoxifen is attributed, in part, to its inability to inactivate AF-1.

The activity of the steroidal antiestrogens such as fulvestrant is very different (Table 2). The steroidal antiestrogens bind to the ER, but because of their long bulky side chains at the 7α and 11β positions, receptor dimerization appears to be sterically hindered (37). There is evidence that ER turnover is increased and that nuclear localization is disrupted with a concomitant reduction in the number of detectable ER molecules in the cell both in vitro and in vivo (38). This is in marked contrast to the stable or increased levels of ER expression associated with tamoxifen and its analogues. In vitro and in vivo studies suggest that as a consequence of ER down-regulation, ER-mediated transcription is completely attenuated because fulvestrant inactivates both AF-1 and AF-2, leading to complete suppression of
the expression of estrogen-dependent genes. Thus, not only is fulvestrant described as a pure antiestrogen, it is also now described as an ERD.

Preclinical Studies

The preclinical characteristics of fulvestrant, which define this compound as a "pure" antiestrogen devoid of estrogen-like activity, have been reviewed extensively (28, 39, 40) and provided the first evidence that fulvestrant may offer a potential therapeutic advantage over tamoxifen. These characteristics include an affinity for the ER approximately 100 times that of tamoxifen, the specific absence of estrogen-like activity on the uterus both in vitro and in vivo, and the capacity to completely block the stimulatory activities of both estrogens and antiestrogens with partial agonist activity, such as tamoxifen. For example, in the rat uterus, in contrast to estradiol and tamoxifen, fulvestrant did not induce genes such as calbindin D, insulin-like growth factor I, vascular endothelial growth factor, and c-fos and, when administered before estradiol or tamoxifen, it completely blocked the induction of these genes by these agents (24). Moreover, fulvestrant has been shown not to block the uptake of $[^3H]$estradiol in the brain, suggesting that fulvestrant does not cross the blood-brain barrier (41) and therefore in humans may not cause the hot flushes associated with the nonsteroidal antiestrogens. The preclinical animal data on the effects of fulvestrant on bone density are conflicting, with reports of reduced cancellous bone volume in one study (42) and no effect on overall density in another (43), and are being investigated further. The absence of estrogenic activity has important consequences for the development of resistance, which is a major concern during tamoxifen therapy. In vitro studies have demonstrated that tamoxifen-resistant cell lines remain sensitive to growth inhibition by fulvestrant (44–46), whereas cells resistant to fulvestrant exhibit early cross-resistance to tamoxifen (47). Also, tamoxifen-resistant tumors remain sensitive to fulvestrant in vivo (48). Preclinical studies in nude mice have shown fulvestrant to suppress the growth of established MCF-7 xenografts for twice as long as tamoxifen and to delay the onset of tumor growth for longer than tamoxifen (48). Taken collectively, these data suggest that fulvestrant is a more effective estrogen antagonist than tamoxifen and is able to produce a longer response in the animal model. Moreover, other animal studies have confirmed the complete absence of uterine-stimulating activity and shown fulvestrant to block the uterotrophic action of tamoxifen (27). In ovariectomized, estrogen-treated monkeys, the extent of involution of the endometrium was similar in animals treated with fulvestrant and in animals in which estrogen treatment was withdrawn (39). Overall, these data indicate that the mode of action and the preclinical effects of fulvestrant are distinct from those of tamoxifen and the newer SERMs and support the concept that fulvestrant represents a novel type of antiestrogen with clinical potential and possibly important implications for the endocrine management of breast cancer in terms of the sequencing of steroidal and nonsteroidal antiestrogen therapies.

Clinical Studies

The data regarding the clinical potential of fulvestrant in patients with breast cancer are also encouraging. Administration of a short-acting, propylene glycol-based formulation of fulvestrant at doses of 6 or 18 mg daily by i.m. injection for 1 week to postmenopausal breast cancer patients before surgery resulted in a reduction in proliferation, as measured by Ki67 labeling index, and a reduction or absence of expression of ER and PgRs in ER-positive tumors (26). Treatment with fulvestrant also resulted in a clinically significant reduction in the expression of the estrogen-regulated gene pS2, but this was unrelated to tumor ER status. Similar experiments with tamoxifen had produced no change in ER expression, slightly increased PgR expression, and a reduction in the Ki67 labeling index after a median 21 days of treatment.

Although fulvestrant reduced ER expression to almost undetectable levels, no other changes suggestive of an endocrine-insensitive phenotype were observed (24). This, coupled with the absence of changes in Ki67 in ER-negative tumors treated with fulvestrant, suggests that the effect is the result of antagonism of estrogen at the ER level. This antiestrogenic effect has been confirmed in a study of premenopausal patients scheduled for hysterectomy for benign gynecological disease who were randomized to receive either 7 consecutive daily doses of the short-acting formulation of fulvestrant or observation before surgery. No increase in endometrial thickness was observed in the fulvestrant-treated patients (49), and there was also significantly lower ER expression in the myometrium of the treated group (50).
In a much larger preoperative study, the antitumor effects of single-dose, long-acting fulvestrant have been compared with those of tamoxifen in postmenopausal primary breast cancer patients before surgery (51). In this study, 201 patients were randomized to receive either fulvestrant over a range of doses (50, 125, or 250 mg) administered i.m., tamoxifen administered p.o. at a dose of 20 mg/day, or a matching tamoxifen placebo for 14–21 days before surgery. A dose-dependent reduction in the levels of ER expression was observed across all three doses of fulvestrant compared with placebo. Also, when the fulvestrant dose normally used clinically (250 mg) was compared with tamoxifen, there was a significantly greater reduction in the ER index for fulvestrant. A dose-dependent reduction in PgR expression was also observed after fulvestrant treatment, which was greater for all three doses of fulvestrant than for tamoxifen, which actually resulted in stimulation of PgR (51) expression. At all three doses, fulvestrant reduced proliferation. These data once again provide evidence that fulvestrant acts as an ERD with clear antiestrogenic and antiproliferative activity (51). Furthermore, the effect on PgR provides evidence of a more complete blockade of this ER-dependent pathway compared with tamoxifen, which increases PgR levels as a result of its partial agonist activity (51).

The clinical efficacy of fulvestrant has also been demonstrated in a small Phase II trial in 19 patients with tamoxifen-refractory disease who received a long-acting monthly i.m. injection starting with 100 mg in the first month and increasing to 250 mg for the second and subsequent months in the absence of local and systemic toxicity. Thirteen patients achieved a clinical benefit, with a median duration of 25 months, with seven patients demonstrating a partial response, and six patients demonstrating stable disease (25, 52). These data clearly confirmed the lack of cross-resistance with tamoxifen observed in preclinical studies. Furthermore, luteinizing hormone and follicle-stimulating hormone levels rose after the patients were removed from tamoxifen but then reached a plateau, suggesting that there is no effect of fulvestrant on the pituitary-hypothalamic axis. Hot flushes and sweats were not induced, and no negative effects were observed on the liver, brain, or genital tract, suggesting that fulvestrant might have fewer side effects in terms of menopausal symptoms than tamoxifen. Thus, fulvestrant at the drug concentrations used in this study was effective as a second-line antiestrogen therapy, supporting a mechanism of action distinct from tamoxifen. In addition, this Phase II study clearly indicated that fulvestrant was well tolerated. Also, comparison with a well-matched historical control group of patients treated with the progestin megestrol acetate suggested a longer duration of response for patients receiving fulvestrant (26 months versus 14 months; Fig. 2; Ref. 53).

### Pharmacokinetics

The pharmacokinetics of multiple-dose fulvestrant administration have been assessed in the Phase III trial described above (25) and more recently in a subset of patients enrolled in a Phase III trial (54). In the Phase II trial, peak levels of fulvestrant occurred a median of 8–9 days after dosing and then declined, but they were still above the projected therapeutic threshold at day 28 (25). Mean $C_{\text{max}}$ (which occurred on day 7) increased from 10.5 ng/ml during the first month to 12.6 ng/ml at month 6. The area under the curve had also increased by 47% at 6 months, suggesting some drug accumulation. In addition, the pharmacokinetic properties of single-dose fulvestrant have been investigated in two multicenter randomized trials in postmenopausal patients with either primary (55) or advanced breast cancer (56), and have been reviewed elsewhere (57). Significantly, the administration regimen (1 × 5 or 2 × 2.5 ml i.m. injections) did not appear to alter the pharmacokinetic profile of fulvestrant (56).

### Phase III Data

The Phase II second-line and preoperative trials reported above provided the initiative for two Phase III studies, one in North America and one in Europe, Australia, and South Africa (ROW), which compared the efficacy and tolerability of fulvestrant (250 mg) administered once monthly with those of the third-generation aromatase inhibitor anastrozole (Arimidex; 1 mg) administered p.o. once daily in postmenopausal women...
whose disease had progressed on or after prior endocrine therapy (58, 59). The vast majority (>96%) of patients across both trials had received prior tamoxifen therapy. The North American trial was a double-blind trial and recruited patients from 83 centers in the United States and Canada, whereas the second trial was an open-label study conducted principally in Europe and recruited patients from 82 centers. Altogether, 400 and 451 patients were analyzed for efficacy in the North American and ROW trials, respectively. The primary end point in both trials was time to disease progression, with secondary end points across both trials that included objective response, duration of response, time to death, tolerability, quality of life, and pharmacokinetics.

The median time to disease progression was numerically longer with fulvestrant compared with anastrozole for both the North American (5.4 versus 3.4 months) and ROW (5.5 versus 5.1 months) trials but was not statistically significant in either trial. The objective response rates were not significantly different in either trial (17.5% for both arms in the North American trial and 20.7% versus 15.7% for fulvestrant and anastrozole, respectively, in the ROW trial). In those patients who responded, median duration of response to fulvestrant and anastrozole was 19.3 and 10.5 months, respectively, in the North American trial and 14.3 and 14.0 months, respectively, in the ROW trial. The clinical benefit rates (defined as complete and partial responses and disease stabilization lasting ≥ 24 weeks) for fulvestrant versus anastrozole were 42.2% versus 36.1% for the North American trial and 44.6% versus 45.0% for the ROW trial. In both trials, the most frequently reported adverse events were gastrointestinal disturbances (e.g., nausea, vomiting, constipation, and diarrhea): 53.4% and 39.7% of patients suffered from at least one gastrointestinal disturbance in the North American and ROW trials, respectively. Overall, the incidence of adverse events was similar for the recipients of anastrozole and fulvestrant in both trials. The withdrawal rates in the fulvestrant and anastrozole groups were low in both trials, with 2.5% versus 2.6% of patients withdrawing due to an adverse event in the North American trial and 3.2% versus 2.2% of patients withdrawing due to an adverse event in the ROW trial (58, 59). Thus, in both studies, fulvestrant was at least as effective as the aromatase inhibitor anastrozole, with a longer duration of response in the North American trial, confirming fulvestrant as an effective treatment in postmenopausal patients with advanced breast cancer recurring or progressing even after tamoxifen therapy. Fulvestrant was also well tolerated and is the first antiestrogen reported to be at least as effective as a new generation aromatase inhibitor. This is of particular significance in light of the fact that two trials comparing anastrozole with tamoxifen in the first-line treatment of breast cancer have shown anastrozole to be superior to tamoxifen both in terms of time to progression and in terms of a lower incidence of thromboembolic events and vaginal bleeding (60, 61).

**Conclusion**

Fulvestrant is clearly the first in a new class of antiestrogen. This novel steroidal ERD is currently being investigated in Phase III trials. Its mode of action (Table 2) and clinical efficacy and side effect profile (Table 3) are distinct from those of tamoxifen, and preliminary data from two Phase III studies show it to be as effective as the third-generation aromatase inhibitor anastrozole as a second-line endocrine therapy in postmenopausal patients who have failed on prior tamoxifen therapy (58, 59).

It is well recognized that patients whose disease progresses after responding to tamoxifen can achieve further responses with third-generation steroidal ( exemestane) and nonsteroidal (anastrozole and letrozole) aromatase inhibitors, and these are currently being investigated as a first-line therapy in metastatic adjuvant and neoadjuvant settings. Fulvestrant is also being investigated in these clinical settings. Thus, fulvestrant not only provides an alternative to tamoxifen, it also offers the opportunity of a further response, at least equivalent to that of anastrozole, in patients who have failed on tamoxifen and has potential as a subsequent therapy after tamoxifen in an adjuvant setting. The results of the ongoing Phase III clinical trials are eagerly awaited, particularly those comparing fulvestrant with tamoxifen as a first-line therapy in advanced disease and the adjuvant studies.

**Open Discussion**

Dr. Per Lonning: You mentioned that the 125-mg dose was abandoned early in the trial because of very low response. Now, we have something like 100 patients with evaluable responses to that dose. Now, if you look at general pharmacokinetics about when you give a drug to a population, 95% confidence intervals for the area under the curve is a ratio of 1:4 for a drug with predictable pharmacokinetics. That tells you that if you double the dose for a drug, a large number of the patients will get similar drug levels with the two doses. So it’s really a concern to me that the response rate to the 125-mg dose was that low, and I think we really need to see the data, because between fulvestrant and Arimidex, there could be a benefit in favor of fulvestrant. It may be by chance.

Dr. Kent Osborne: In the American study there are some responses to the lower dose. There are pharmacokinetic studies with those doses of fulvestrant. I don’t think the confidence intervals are as broad as you might have predicted. You’re not having to worry about bioavailability, which is so different in lots of patients, with an i.m. injection. I’ve asked the pharmacokinetics researcher what would happen if you double the dose.

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<tr>
<th>Table 3</th>
<th>Summary of clinical efficacy and side effect profiles of fulvestrant and tamoxifen</th>
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<td><strong>Clinical activity</strong></td>
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<td>Neoadjuvant</td>
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<td>Tamoxifen resistance</td>
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<td>A agonist activity on uterus</td>
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<td>Bone density</td>
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* ND, not determined; ↓, a favorable change; =, no change; NT, not tested.
even further to 500 mg, which is the dose I favor. He said the serum levels would double in the majority of patients.

**Dr. Lonnning:** The 1:4 ratio with the confidence intervals in general relates to drugs that are completely absorbed. If you have drugs with more unpredictable absorption like megestrol acetate, you get a 1:10 ratio. I’ve never seen a drug with a smaller confidence interval than 1:4.

**Dr. Anthony Howell:** We published the pharmacokinetics, and they’re in that *British Journal of Cancer* paper (Br. J. Cancer, 74: 300–308, 1996). It did show relatively small confidence intervals, and there was also accumulation with time. With the first injection you achieved what were thought to be therapeutic biologically effective levels at that time, or else these studies would never have gone on at all.

**Dr. Osborne:** Having granted that, though, I think this dose issue is a real issue, primarily because of that 125-mg dose. The fact that there were very few responses tells me that we’re pretty close to the ineffective dose, and we may not be at the optimal dose, particularly in premenopausal women in whom there is competing estrogen to bind the receptor. So I think it’s a very important issue and deserves more study.

**Dr. Kathleen Pritchard:** We can give them a couple of injections at 2-week intervals for the first month.

**Dr. Osborne:** I’m just hoping that the insurance companies don’t read the fine print, because that’s what I’m going to do in my ad hoc study—give them a double dose at first to get the level up there.

**Dr. Howell:** That was the argument with tamoxifen, obviously, to give a loading dose of 40 mg qds.

**Dr. Alan Wakeling:** Tell us about that tamoxifen study with the loading dose.

**Dr. Osborne:** It worked, but there you’re dealing with a drug that has partial agonist activity, and that strategy may counteract that early tickle, as Craig Jordan calls it. I’m not sure what that means in a molecular sense, but he says when you tickle the receptor initially that you may get this agonist effect that can lead to tumor growth.

**Dr. Howell:** We don’t have hard data on whether the loading dose strategy prevented any flares, but we don’t see very many flares anyway.

**Dr. Pritchard:** If you’re taking this drug into the adjuvant setting, you might make the argument that it doesn’t matter, because you’re going to get a level of what you need in a few months anyway. Or you could make the argument that it’s that initial time period that matters the most and this is a crucial issue, just as it probably is in metastatic disease.

**References**

Preliminary Experience with Pure Antiestrogens

Anthony Howell

_Clin Cancer Res_ 2001;7:4369s-4375s.