The Oncologist®
Breast Cancer

Fulvestrant (Faslodex®)—How to Make a Good Drug Better

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Key Words. Breast cancer • Dose–response relationship • Drug • Estrogen receptor • Fulvestrant • Pharmacokinetics

ABSTRACT

Fulvestrant (Faslodex®; AstraZeneca Pharmaceuticals, Wilmington, DE) is an estrogen receptor (ER) antagonist with a novel mode of action; it binds, blocks, and increases degradation of ER. Fulvestrant (at the approved dose [250 mg/month]) is at least as effective as anastrozole (1 mg/day) in the treatment of postmenopausal women with hormone receptor–positive advanced breast cancer (HR^+ ABC) progressing or recurring on antiestrogen therapy, and is also an active first-line treatment. Although fulvestrant (250 mg/month) is clearly effective, it takes 3–6 months to achieve steady-state plasma levels. Steady-state concentrations are approximately twofold higher than those achieved with a single dose; reaching this earlier, for example, via a loading-dose (LD) regimen (250 mg/month plus 500 mg on day 0 and 250 mg on day 14 of month 1), may allow responses to be achieved more quickly and limit the possibility of early relapse.

Fulvestrant high-dose (HD) regimens (500 mg/month) offer the possibility of greater antitumor activity, because (a) ER downregulation is a dose-dependent process (an approximately 70% reduction is observed with a single 250 mg dose of fulvestrant) and (b) evidence correlates greater ER downregulation with superior efficacy. A fulvestrant HD regimen offers the potential of achieving near 100% ER downregulation. There is also potential to increase fulvestrant–ER binding by reducing plasma estrogen levels, for example, with concomitant aromatase inhibitor treatment.

Several ongoing trials use LD, HD, and combination regimens; results from these studies are awaited with interest. Meanwhile, fulvestrant (250 mg/month) remains a valuable additional endocrine treatment for postmenopausal women with HR^+ ABC recurring or progressing on antiestrogen therapy. ***The Oncologist*** 2007;12:774–784

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

Approximately 75% of breast tumors in postmenopausal women are estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive and these patients are therefore candidates for endocrine treatment [1]. Tamoxifen was the mainstay of endocrine treatment for these patients for many years [2], but recently the third-generation aromatase inhibitors (AIs) have started to be used ahead of tamoxifen in the first-line advanced [3] and adjuvant [4] settings because of their superior efficacy and tolerability profiles. Tamoxifen continues to be commonly used, but many clinicians use it further down the treatment sequence. Despite these changes in clinical practice, most patients with advanced breast cancer ultimately experience a relapse or disease progression following endocrine treatment. As a result there is a need for new, non–cross-resistant, well-tolerated agents that can be integrated into the endocrine treatment sequence.

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This may delay the need for the use of less well-tolerated cytotoxic drugs.

Fulvestrant (Faslodex®; AstraZeneca Pharmaceuticals, Wilmington, DE) is a new ER antagonist with no estrogen agonist effects [5] and a novel mode of action; it binds, blocks, and increases degradation of ER protein, leading to an inhibition of estrogen signaling through the ER [6, 7]. Because of its mode of action, there is potential for enhancing the efficacy of this agent by using alternative dosing regimens. This and the potential of fulvestrant in combination regimens are the focus of this review and discussion.

Established Clinical Efficacy and Tolerability of Fulvestrant

Tamoxifen-Resistant Advanced Breast Cancer

Fulvestrant is the only endocrine therapy targeting the ER that has been shown to have efficacy in tamoxifen-resistant disease in phase III clinical trials [8, 9]. Trials 0020 and 0021 compared the efficacy and tolerability of fulvestrant (250 mg/month, i.m. injection) with those of anastrozole (1 mg/day, orally) in the treatment of postmenopausal women with advanced breast cancer whose disease had progressed or relapsed on prior antiestrogen therapy. A prospectively planned combined analysis of the data from these trials showed that fulvestrant was at least as effective as anastrozole in terms of time to progression (TTP) (5.5 months versus 4.1 months, respectively) [10]. Objective response (OR) (partial or complete response) and clinical benefit (CB) (OR or stable disease [SD] for ≥24 weeks) rates were also similar, as were the median durations of response. A retrospective analysis of the combined data from these trials showed that these drugs had similar efficacies in patients with and without visceral metastases [11]. In a subsequent combined analysis of survival data, the median overall survival was not significantly different between treatments [12].

Both drugs were well tolerated in these trials, with only approximately 1% of patients in each group withdrawing as a result of treatment-related adverse events (AEs). Irrespective of causality, the most common AEs in both groups were hot flashes, nausea, asthenia, pain, and headache. The fulvestrant injection was well tolerated locally, with injection-site reactions occurring in only about 1% of courses [10]. Of the seven AEs prospectively defined for statistical analysis (gastrointestinal disturbances, hot flashes, vaginitis, weight gain, thromboembolic disease, urinary tract infection, and joint disorders), only joint disorders differed significantly between groups (5.4% versus 10.6% for fulvestrant and anastrozole, respectively; $p = .0036$).

Based on these trial results, fulvestrant received regulatory approval in many countries as a second-line treatment for postmenopausal women with hormone-sensitive advanced breast cancer after progression or relapse on antiestrogen therapy.

First-Line Treatment of Advanced Breast Cancer

A double-blind, randomized phase III trial (trial 0025) later compared fulvestrant (250 mg/month) with tamoxifen (20 mg/day) in the first-line treatment of postmenopausal women with advanced breast cancer [13]. TTP was not significantly different in the fulvestrant and tamoxifen groups, but fulvestrant did not meet the criteria for noninferiority to tamoxifen in the intent-to-treat population. In these patients tamoxifen was associated with significant benefits in terms of the CB rate (54.3% versus 62.0%; $p = .026$), time to treatment failure (5.9 months versus 7.8 months; $p = .026$), and overall survival (36.9 months versus 38.7 months; $p = .04$). However, in a prospectively planned analysis of patients with ER-positive and/or PgR-positive tumors (approximately 80% of the population), that is, those most likely to respond to endocrine therapy, the median TTP was 8.2 months for fulvestrant and 8.3 months for tamoxifen, while the CB and OR rates and overall survival were also similar between groups. The results of this trial were unexpected given the fact that the third-generation AIs are superior to tamoxifen in the first-line setting [14, 15] and that fulvestrant is at least as effective as anastrozole in the second-line setting [10].

In trial 0025, fulvestrant was as well tolerated as tamoxifen in terms of treatment-related AEs, and the most common AEs (irrespective of causality) in both groups were nausea, asthenia, vasodilation, pain, and bone pain. Of the four prospectively defined AEs in this trial (gastrointestinal disturbances, hot flashes, thromboembolic disease, and vaginitis) only hot flashes differed between groups (17.7% versus 24.7% for fulvestrant and tamoxifen, respectively; $p = .0501$).

Opportunities for Enhancing the Efficacy of Fulvestrant

Historically, it has been common practice for clinical experience to play a role in the evolution and optimization of the use of licensed anticancer treatments. For instance, various loading-dose (LD) and high-dose (HD) regimens of oral tamoxifen have been evaluated in patients with advanced breast cancer [16–18]. For example, one such study included 37 patients and tested three different LD schedules of tamoxifen: 20 mg/m^2 twice daily (BID), 40 mg/m^2 BID, and 80 mg/m^2 BID for 7 days, followed by 20 mg/m^2 once daily thereafter, as well as two different 20 mg/m^2 per day regimens [16]. At 20 mg/m^2 BID, three of four patients

reached steady state within 1 week. All four patients receiving the 40 mg/m^2 BID dose were at steady state within 1 week and all were within the minimum range known to be associated with response (70–150 ng/ml) by 72 hours. In two patients receiving the 80 mg/m^2 BID dose, levels known to be associated with a response were observed within 3 hours. In contrast, steady-state values were only obtained after 16 weeks' chronic dosing in patients receiving the standard schedule of 20 mg/m^2 per day. Steady-state levels of tamoxifen increased with dose. Unfortunately, in this study, time to response was only analyzed for the overall population (median, 6 weeks) and so the shorter time to steady state/higher steady-state levels cannot be correlated with any change in time to response. Interestingly, blood tamoxifen levels known to be associated with response were still present 21 days after discontinuation, and tamoxifen was still detectable 6 weeks after treatment. Consequently, the authors suggested that it may be prudent to delay ER sampling of the tumor for 4 weeks after treatment discontinuation to reduce the risk for obtaining false-negative results [16]. The different treatment schedules were reasonably well tolerated, although one patient receiving the highest LD experienced paroxysmal atrial tachycardia and two patients experienced flare reactions (receiving 20 mg/m^2 BID and 20 mg/m^2 per day, respectively). Other side effects included headache, hot flashes, and nausea.

A second study, including 70 patients, showed that an LD regimen of 160 mg on day 1 followed by 20 mg/day thereafter was well tolerated [17]. The authors noted that, in patients receiving the standard dose (20 mg/day), the minimum time to response was 6–8 weeks, whereas in those receiving the LD regimen, one third of patients responded within 4 weeks. An LD regimen of 160 mg on days 1 and 2 followed by 30 mg/day thereafter was later evaluated in a pharmacokinetic study in 14 patients. This dose schedule allowed achievement of steady-state tamoxifen levels within 1–2 weeks (steady-state metabolite levels were attained after ≥4 weeks of dosing) [18].

Whilst 250 mg/month of fulvestrant is a clinically effective dose, experience suggests that there may be opportunities for further enhancing its efficacy with the use of alternative dosing regimens. Its novel mode of action also makes it an attractive agent for use in combination with other agents such as AIs or trastuzumab. Because the 250 mg dose of fulvestrant is well tolerated, there is an opportunity to use LD (500 mg day 0, 250 mg days 14 and 28 of month 1, and 250 mg every 28 days thereafter) or HD (500 mg on days 0, 14, and 28, and 500 mg every 28 days thereafter) regimens (Fig. 1).

Fulvestrant LD Regimens—Potential for Shorter Time to Steady State and Lower Risk for Early Progression?

As endocrine agents suppress the growth of hormone-responsive cancer cells as opposed to having a direct cytotoxic effect, it may take more time to see a treatment response with endocrine therapy than with chemotherapy [19]. Indeed, it has been noted that some patients may show signs of progression early on in endocrine treatment (that is, during the first 2 months), but if maintained on treatment they then go on to achieve ORs when the drug reaches therapeutic levels. During the early weeks of endocrine therapy, therefore, the clinician may be faced with the dilemma of whether or not to continue therapy or change to another treatment (for example, chemotherapy). In patients with hormone receptor–positive tumors, OR rates may be lower with endocrine treatment than with chemotherapy, but overall CB rates are similar. This is of importance, because SD on an endocrine therapy gives similar survival benefit to an OR [20–22]. Furthermore, ORs and SD on endocrine therapy are, on average, more durable than those achieved with chemotherapy [23].

Pharmacokinetic and clinical data from phase III trials of fulvestrant have led to speculation that there may be scope to optimize its activity via the use of an LD regimen. In trials 0020 and 0021 it was determined that steady-state plasma concentrations of fulvestrant are approximately twofold higher with repeated administration than those achieved following a single dose, and that it can take 3–6 months for fulvestrant to reach steady-state levels at the 250 mg/month dose [24]. Encouragingly, the pharmacokinetic behavior of fulvestrant observed in these trials closely resembled the behavior predicted in pharmacokinetic models (Fig. 2) [24]. As a result of this, models have since been developed to estimate the pharmacokinetic behavior of fulvestrant LD and HD regimens (Fig. 3). Both models predict that these regimens may help fulvestrant reach steady-state levels more rapidly. Furthermore, a preliminary pharmacokinetic study of the LD regimen has shown that steady-state fulvestrant levels were achieved within 1 month of treatment (AstraZeneca, data on file). Although the exact therapeutic threshold for fulvestrant has not been determined, attainment of steady state earlier on in treatment may have the potential of reducing the time taken to achieve therapeutic levels. Ongoing clinical trials will determine whether the use of an LD regimen also reduces the time taken to achieve a response. However, it is important to note that despite the time taken to achieve steady state, in trials 0020 and 0021 the 250 mg/month dosage of fulvestrant was associated with a median time to response and TTP similar to those of anastrozole [10, 25]—a drug that takes only approximately

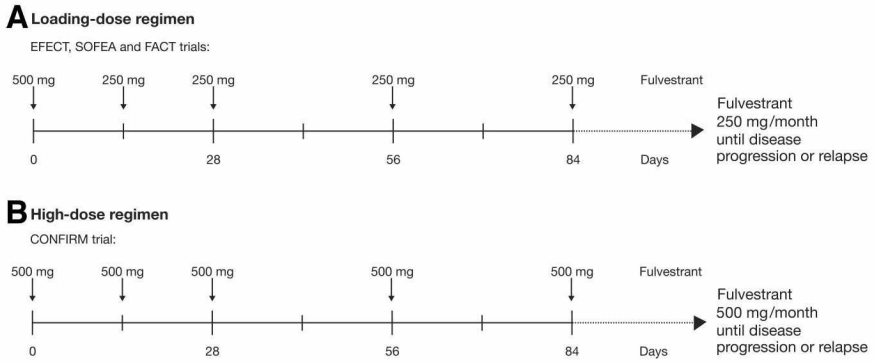


Figure 1. Treatment schedules in loading-dose (**A**) and high-dose (**B**) fulvestrant regimens and examples of trials using such regimens.

Abbreviations: CONFIRM, Comparison of Faslodex in Recurrent Metastatic Breast Cancer; EFECT, Evaluation of Faslodex and Exemestane Clinical Trial; FACT, Fulvestrant and Anastrozole Clinical Trial; SOFEA, Study of Faslodex With or Without Concomitant Arimidex Versus Exemestane Following Progression on Aromatase Inhibitors.

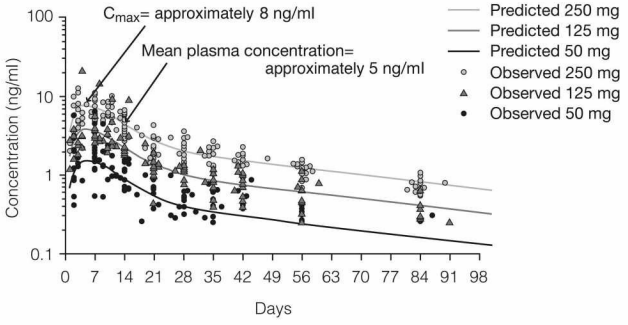


Figure 2. Fulvestrant single-dose pharmacokinetics: comparison between modeled and observed behavior. From Robertson JF, Odling-Smee W, Holcombe C et al. Pharmacokinetics of a single dose of fulvestrant prolonged-release intramuscular injection in postmenopausal women awaiting surgery for primary breast cancer. Clin Ther 2003;25:1440–1452, with permission from Excerpta Medica, Inc.

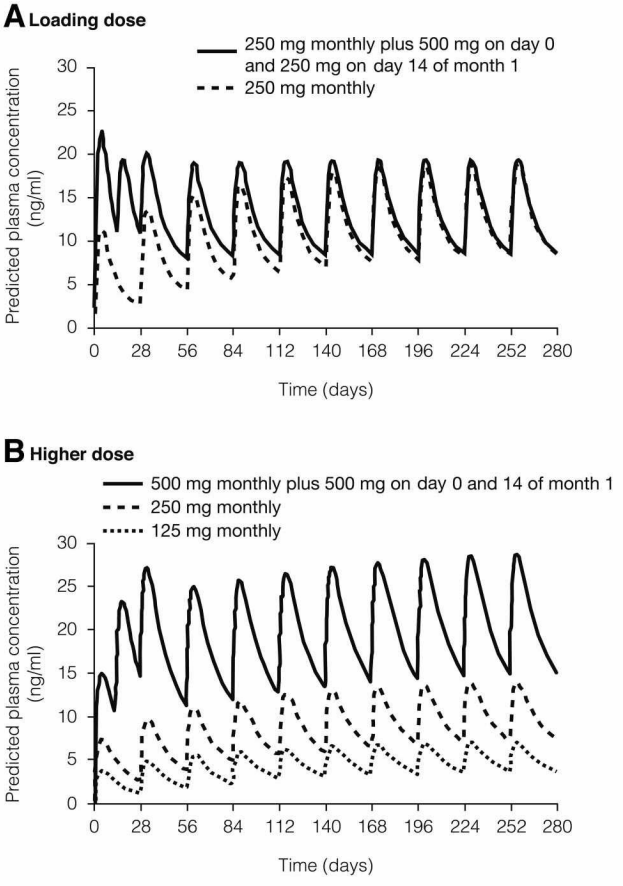


Figure 3. Pharmacokinetic models for loading-dose (**A**) and high-dose (**B**) fulvestrant regimens.

7 days to reach steady-state levels and leads to maximal estrogen suppression within 2–4 days [26]. It is notable that some patients receiving fulvestrant respond very quickly to treatment, suggesting there may be some level of interpatient variability in sensitivity to fulvestrant [25].

Early attainment of therapeutic levels through the use of an LD regimen may be of particular value for those patients at risk for progressing early on during endocrine treatment. It is important to note, however, that no direct relationship among plasma level, ER downregulation, and clinical efficacy has been defined as yet. Nonetheless, the higher rate of early progression/relapse noted in the fulvestrant group in trial 0025 may theoretically be related to the time taken for this drug to reach steady-state plasma concentrations and a subsequent potential delay in maximal ER downregulation [24]. However, the dose and schedule were the same as used in trial 0020, in which fulvestrant was clearly as effective as anastrozole. A possible explanation for this difference in progression rate between studies is that a small number of patients get a withdrawal response when discontinuing tamoxifen [27]. Therefore, in trials 0020 and 0021, in which patients had previously discontinued tamoxifen because of acquired resistance, it is possible that this tamoxifen-withdrawal response compensated for any delay in achieving a

therapeutic dose of fulvestrant. In contrast, in trial 0025, patients were receiving fulvestrant as first-line endocrine therapy and so no carryover effect from previous treatment would have occurred. Thus, especially in the first-line setting, the use of an LD regimen may, in theory, help prevent patients from relapsing early on in treatment. However, it must be noted that approximately 30%–40% of hormone receptor–positive tumors will show de novo resistance and that these patients will still relapse early on in treatment even if steady-state plasma levels have already been achieved, as was noted in the anastrozole group in trials 0020 and 0021.

Ongoing Trials Including Fulvestrant LD Regimens

The International, phase III Evaluation of Faslodex and Exemestane Clinical Trial (EFECT) is comparing the LD fulvestrant regimen (plus exemestane placebo) with exemestane (25 mg/day, orally, plus fulvestrant placebo) in postmenopausal women whose disease has recurred or progressed after prior nonsteroidal AI therapy. First results from this trial have recently been reported; the median TTP was 3.7 months for both treatments [28]. OR (7.4% versus 6.7%) and CB (32.2% versus 31.5%) rates were also similar for LD fulvestrant and exemestane, respectively. Fulvestrant plasma level data confirmed that steady state was achieved within 1 month with this treatment regimen. In addition, the phase III Study Of Faslodex with or without concomitant arimidex versus Exemestane following progression on Aromatase inhibitors (SOFEA) is comparing the efficacy of fulvestrant alone with that of fulvestrant plus anastrozole, with a comparison with exemestane being a secondary aim. An LD regimen of fulvestrant is being used in both the monotherapy and combination therapy arms of this trial. However, none of the above trials actually compare the LD regimen with the approved dosing schedule—such comparisons are included in the Comparison of Faslodex in Recurrent Metastatic Breast Cancer (CONFIRM) and Faslodex INvestigation of Dose evaluation in Estrogen Receptor-positive advanced breast cancer (FINDER) 1 and 2 studies. Further information on these studies is provided below.

Fulvestrant HD Regimens—Potential for Greater ER Downregulation and Greater Efficacy?

Correlation of ER Downregulation with Fulvestrant Dose

Unlike the AIs, which reach a peak of pharmacological activity at established clinical doses (that is, >90% suppression of estradiol) [26], there may be potential for greater biological activity with the use of higher doses of fulvestrant. Dose-dependent effects of fulvestrant on ER downregulation have been demonstrated in two previous studies.

In study 0018, the effects of a single i.m. dose of long-acting fulvestrant (50 mg, 125 mg, or 250 mg), continuous daily tamoxifen, or placebo for 14–21 days prior to surgery were compared in patients with primary breast tumors. The effects of these treatments on ER and PgR protein expression were assessed by immunohistochemistry and reported as ER and PgR indices. All fulvestrant doses produced statistically significant reductions in ER expression compared with placebo (Fig. 4). At the 250 mg dose, the fulvestrant-induced reduction was significantly greater than that observed with tamoxifen [29]. Significant reductions in PgR expression were also observed with the 125 mg and 250 mg fulvestrant doses compared with placebo. In contrast, tamoxifen resulted in a significant increase in PgR expression, a finding attributed to its partial agonist effects and further emphasizing the differences in mode of action between fulvestrant and tamoxifen [29]. However, the level of ER downregulation appeared incomplete (approximately 70%) following a single 250 mg dose of fulvestrant compared with levels achieved in earlier studies. Furthermore, authors of a sequential biopsy study have recently reported that even after 6 months of fulvestrant treatment, ER is still present in the tumor (at approximately 50% of baseline levels) [30].

Dose-dependent effects on ER levels were also seen in an earlier study (study 0002) of the effects of daily s.c. injections of short-acting fulvestrant (either 6 mg or 18 mg) for 7 days prior to surgery for primary breast cancer in 56 postmenopausal women [31]. In patients with ER-positive tumors (28/56), overall fulvestrant treatment caused a significant reduction in the median ER index (0.73 versus 0.02 pre- and post-treatment, respectively; $p < .001$) and the median PgR index was reduced from 0.50 to 0.01 post-treatment ($p < .05$). Greater ER downregulation was observed with fulvestrant at the 18 mg/day dosage (0.73 versus 0.01 pre- and post-treatment, respectively; $p < .01$) than with the 6 mg/day dosage (0.6 versus 0.06 pre- and post-treatment, respectively; $p < .05$) [31].

Because ER downregulation appears to be a dose-dependent process, it may be possible to enhance ER downregulation by further increasing fulvestrant steady-state plasma concentrations. Single doses of fulvestrant 50 mg, 125 mg, and 250 mg resulted in mean plasma concentrations of 1 ng/ml, 2.5 ng/ml, and 5.0 ng/ml, respectively [32], whereas, pharmacokinetic data from trials 0020 and 0021 demonstrated that multiple dosing of fulvestrant at 250 mg resulted in steady-state (trough) plasma levels in the range of 6–9 ng/ml [24]. In line with this, 18 mg/day of the ful-

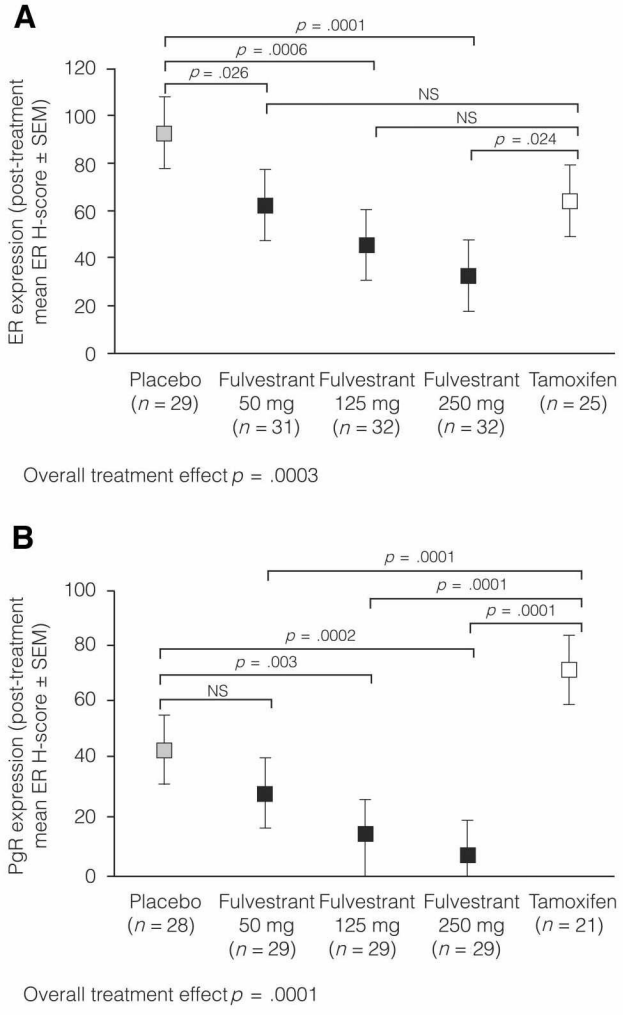


Figure 4. Effects on cellular ER (**A**) and PgR (**B**) levels with fulvestrant (single 250 mg injection) and tamoxifen (20 mg/day for 14–21 days) treatment. From Robertson JF, Nicholson RI, Bundred NJ et al. Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5- pentafluoropentylsulfinyl)-nonyl]estra-1,3,5, [10]-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. Cancer Res 2001;61:6739–6746, with permission of the American Association for Cancer Research.

Abbreviations: ER, estrogen receptor; NS, not significant; PgR, progesterone receptor; SEM, standard error of the mean.

vestrant short-acting formulation results in a mean plasma fulvestrant concentration of approximately 23 ng/ml, whereas 6 mg/day of this formulation results in a mean plasma fulvestrant concentration of approximately 7 ng/ml. Indirect comparison across these two studies suggests that higher mean fulvestrant plasma concentrations may lead to greater ER downregulation (Fig. 5), thereby leading to an expected increase in the downregulation of ER signaling. The pharmacokinetic model of the HD regimen compared with the fulvestrant regimens of 125 mg/month or 250 mg/month also suggests that higher mean plasma fulvestrant

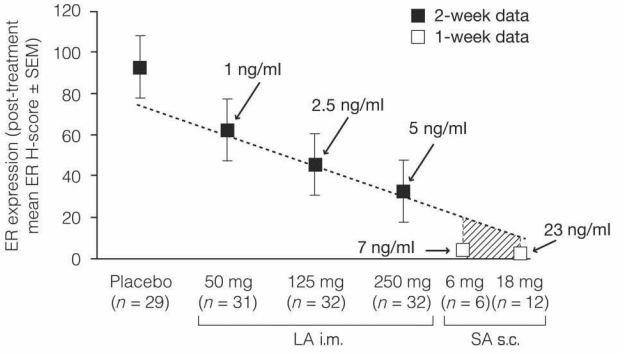


Figure 5. ER downregulation following single doses of fulvestrant long-acting (LA) and short-acting (SA) formulations. Data shown are 2 weeks and 1 week postdose, respectively; the mean plasma drug concentrations are indicated for the same time points. The shaded area represents the likely ER expression predicted for a single 500 mg dose of fulvestrant, which pharmacokinetic modeling suggests will achieve a mean plasma level of approximately 14 ng/ml [29, 31].

Abbreviations: ER, estrogen receptor; SEM, standard error of the mean.

levels will be achieved (approximately 20 ng/ml) and steady state will be reached more quickly with the high fulvestrant dose (Fig. 3).

Thus, there would appear to be an opportunity to improve the activity of fulvestrant either through attaining a therapeutic dose earlier or through delivering a higher dose that would result in a higher concentration of fulvestrant, which in turn would increase downregulation of ER.

Correlation of ER Downregulation with Clinical Efficacy

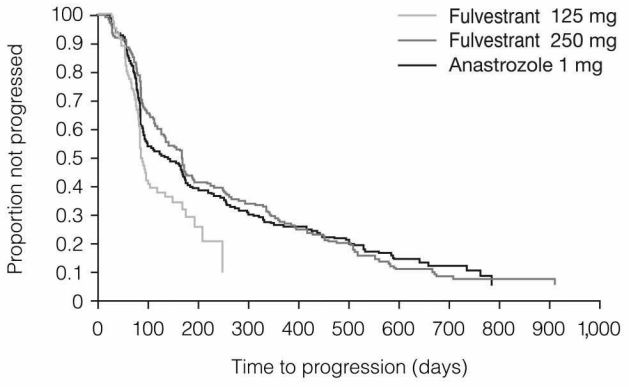
Although the exact relationship between the level of ER downregulation and clinical efficacy is yet to be determined, there is some evidence to suggest that greater ER downregulation may be associated with better treatment response. For example, a greater reduction in ER level after 6 weeks of tamoxifen treatment was associated with a significantly better quality of response (OR versus SD/disease progression) in 51 patients receiving treatment for primary breast cancer [33]. Gamma linolenic acid (GLA), an agent known to modulate the structure and function of steroid hormone receptors, has been shown to have selective antitumor activity. In a study comparing the activity of tamoxifen alone with tamoxifen in combination with GLA, patients receiving the combination had significantly greater reductions in tumor ER levels at 6 weeks ($p = .026$) and 6 months ($p = .019$) and significantly faster clinical responses ($p = .010$) than those receiving tamoxifen alone [34]. Similarly, in ER-positive human breast cancer xenografts, mice receiving GLA in combination with tamoxifen

had significantly greater ER reductions than mice receiving tamoxifen alone [35]. These data suggest that GLA may enhance tamoxifen-induced ER downregulation, with a resultant effect on time to response. Furthermore, results of a study examining the relationship between ER downregulation and response to fulvestrant treatment were recently presented at the San Antonio Breast Cancer Symposium. Significant ER downregulation was seen at 4–6 weeks in patients experiencing CB ($n = 25$) with fulvestrant, but not in those progressing de novo ($n = 5$) [30, 36]. However, there appeared to be no obvious relationship between the level of ER downregulation at 4–6 weeks and the median TTP.

Correlation of Efficacy with Fulvestrant Dose

Both trials 0020 and 0021 originally included a 125 mg/month fulvestrant treatment arm. However, at a preliminary analysis (performed by an independent data monitoring committee), after patients had received 3 months of fulvestrant treatment at the 125 mg dose, no ORs had occurred and so this arm was dropped. Subsequent analysis showed that patients receiving the 125 mg dose of fulvestrant progressed more quickly than those receiving the 250 mg dose (Fig. 6). Furthermore, results from a previous study assessing the pharmacokinetic behavior of different single doses of fulvestrant demonstrate that plasma concentrations are lower following a single 125 mg dose of fulvestrant (mean plasma fulvestrant concentration of approximately 2.5 ng/ml) than with the 250 mg dose (mean plasma fulvestrant concentration of approximately 5 ng/ml) [32]. Therefore, it is expected that steady-state plasma levels in patients receiving the 125 mg/month dosage of fulvestrant would also be lower than those observed in patients receiving the 250 mg/month dosage of fulvestrant. Because patients receiving the 125 mg dose of fulvestrant showed a lower response rate and shorter TTP than those receiving the 250 mg dose, it seems possible that efficacy may be improved further with dosages above 250 mg/month [8, 9].

A further strand of support for this hypothesis can be drawn from presurgical studies of fulvestrant in premenopausal women. One such study, in which premenopausal women received a single dose of fulvestrant of 250 mg while awaiting surgery for primary breast cancer, reported no effect on ER, PgR, or Ki67 levels with fulvestrant compared with placebo [37]. This is in contrast to results from a similar study in postmenopausal women, in which significant effects on these markers were observed with the same fulvestrant dose [29]. Fulvestrant is known to compete for the ER on virtually a one-to-one basis with estradiol, and premenopausal women have almost logarithmically higher systemic estradiol levels than postmenopausal women. For this reason, it has been hypothesized that higher fulvestrant doses may be required for activity in premenopausal patients. Recent results of a study comparing the biological effects of a single 750 mg dose of fulvestrant with tamoxifen at a dosage of 20 mg/day for 14–16 days before surgery support the idea that a higher fulvestrant dose may improve efficacy in the premenopausal setting [38, 39]. Here, both fulvestrant and tamoxifen significantly reduced ER levels, although the reduction in ER was significantly greater in the fulvestrant group. Both agents also significantly reduced proliferation, and fulvestrant, but not tamoxifen, significantly reduced PgR levels [38].



Statistical comparisons

Anastrozole 1 mg vs. fulvestrant 125 mg: HR: 0.63; 95.14% CI: 0.47, 0.84; $p = 0.0018$
Fulvestrant 250 mg vs. anastrozole 1 mg: HR: 0.95; 95.14% CI: 0.81, 1.10; $p = 0.4596$
Fulvestrant 250 mg vs. fulvestrant 125 mg: HR: 0.59; 95.14% CI: 0.44, 0.80; $p = 0.0005$

Figure 6. Combined analysis of time to progression data from trials 0020 and 0021. From Robertson JF, Osborne CK, Howell A et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women—a prospective combined analysis of two multicenter trials. Cancer 2003;98:229–238, with permission of Wiley-Liss Inc., a subsidiary of John Wiley & Sons, Inc.

Ongoing Trials Evaluating Fulvestrant HD Regimens

The international, phase III, CONFIRM trial, will compare 500 mg/month of fulvestrant (plus 500 mg on day 14 of month 1) with 250 mg/month of fulvestrant in postmenopausal women with ER-positive advanced breast cancer progressing or relapsing after previous endocrine therapy. This trial should also determine whether a higher dose and greater ER downregulation correlate with superior clinical efficacy. Two smaller phase II studies based in Japan (FINDER 1) and the rest of the world (FINDER 2) will also compare the LD, HD, and approved-dose regimens of fulvestrant. Fulvestrant HD regimens are also being used in two combination treatment trials mentioned later in this review.

Fulvestrant Plus an AI—Decreasing Estradiol Levels via Combination Therapy

As fulvestrant competes with estradiol for binding of the ER, reducing plasma estrogen levels could increase fulvestrant–ER binding and potentially increase its efficacy. Aromatization of androgens is the major source of estradiol in postmenopausal women and the new third-generation AIs are highly effective at reducing estradiol levels in such patients [40]. Combination treatment using two agents that have different ways of abrogating estrogen signaling, such as fulvestrant and an AI, could therefore potentially result in greater antitumor activity.

Support for this hypothesis comes from preclinical studies in ovariectomized athymic mice bearing tumors of ER-positive breast cancer cells stably transfected with the aromatase gene [41, 42]. In this system, fulvestrant plus letrozole more effectively suppressed xenograft growth than either agent alone [41]. This was in contrast to results seen with tamoxifen plus letrozole, which was found to have similar activity to tamoxifen alone and to be less active than letrozole alone [41], in line with what has been observed clinically with this combination [43]. Furthermore, in addition to being highly effective at inhibiting xenograft growth, combination treatment with fulvestrant plus letrozole prevented increases in erbB-2 and activation of mitogen-activated protein kinase, suggesting that this may delay the development of hormone-independent signaling pathways regulating proliferation [42, 44].

Ongoing Trials Including Fulvestrant Plus Anastrozole Combination Treatment Arms

Several trials are evaluating fulvestrant plus anastrozole combination regimens, including the previously mentioned SOFEA trial. The phase III Southwest Oncology Group (SWOG) study 0226 is comparing the efficacy of fulvestrant, at a dosage of 250 mg/month, plus anastrozole, at a dosage of 1 mg/day, with anastrozole (1 mg/day) as a first-line treatment for postmenopausal women with ER-positive advanced breast cancer. Selected patients in the anastrozole arm will be crossed over to fulvestrant treatment at progression in this study. Postmenopausal patients (and premenopausal patients receiving goserelin treatment) will be included in the phase III Fulvestrant and Anastrozole Clinical Trial (FACT). This trial is comparing a fulvestrant LD regimen plus anastrozole 1 mg/day with anastrozole (1 mg/day) in patients with ER-positive advanced breast cancer. A further phase II preoperative study (study 0057) will compare the antitumor activities of a single 500 mg dose of fulvestrant plus anastrozole (1 mg/day) (for 14–21 days prior to surgery) with fulvestrant (500 mg) or anastrozole (1 mg/day) alone in postmenopausal patients with ER-positive primary breast cancer.

Fulvestrant Alone and in Combination with Trastuzumab in Patients with HER-2–Positive Disease

ER–growth factor receptor crosstalk is one of the mechanisms by which tumors may develop resistance to endocrine treatments. Since fulvestrant reduces cellular ER levels, it may also limit the possibility for receptor crosstalk and thus may potentially delay the onset of endocrine resistance. There are data to suggest crosstalk specifically between the human epidermal growth factor receptor (HER)-2 and ER signal transduction pathways [45]. Therefore, there is potential to further delay the onset of resistance with the use of combination treatment strategies targeting both the ER and, for example, HER-2. HER-2 is expressed in about 20%–30% of all primary breast cancers [46], and HER-2–positive status is associated with more aggressive tumor behavior and poor patient prognosis [47]. There is also evidence linking HER-2 overexpression with tamoxifen resistance [48, 49] as well as resistance to chemotherapy regimens based on cyclophosphamide, methotrexate, and 5-fluorouracil [50].

The results of a preclinical study investigating the effects of fulvestrant and tamoxifen in HER-2–expressing tumor xenografts have been reported [51]. Growth of HER-2–negative MCF-7 and ZR75–1 xenografts was significantly inhibited by both tamoxifen and fulvestrant. However, HER-2–expressing tumors were largely resistant to tamoxifen but retained significant sensitivity to fulvestrant. Tamoxifen sensitivity was restored by the combination of tamoxifen and trastuzumab, but fulvestrant plus trastuzumab had a more potent antitumor effect [51]. In support of this observation, evidence from the Compassionate Use Program suggests that fulvestrant monotherapy may also be active in patients with HER-2–positive tumors [52, 53]. For example, in a pooled, retrospective analysis of data from 339 patients treated at eight centers from the Compassionate Use Program, 15 of the 37 patients (40.5%) with HER-2–positive disease gained CB with fulvestrant treatment [53]. Trials of fulvestrant (HD) alone and in combination with trastuzumab in patients with HER-2–positive tumors are currently under way. Encouraging results have recently been reported from the TrAstuzumab in Dual HER-2–positive Metastatic breast cancer (TAnDEM) study [54], supporting the rationale for such combination treatment strategies. This phase III study compared the efficacy and safety of trastuzumab plus anastrozole with those of anastrozole alone in postmenopausal women with HER-2–positive and ER-positive and/or PgR-positive metastatic

breast cancer. Combination treatment resulted in a significantly longer progression-free survival time (4.8 months versus 2.4 months; $p = .0016$) and TTP (4.8 months versus 2.4 months; $p = .0007$) and significantly higher CB (42.7% versus 27.9%; $p = .026$), and OR (20.3% versus 6.8%; $p = .018$) rates.

Summary

Fulvestrant (250 mg/month) is an effective and well-tolerated treatment for postmenopausal women with advanced breast cancer progressing on prior tamoxifen and is the first antiestrogen to demonstrate efficacy in this setting. Fulvestrant is active in the first-line setting in patients with ER-positive and/or PgR-positive tumors and there is also some evidence to suggest that it may be active as monotherapy in patients with HER-2–positive disease. Thus, fulvestrant is already proving to be a valuable addition to the endocrine treatment sequence for postmenopausal women with advanced breast cancer.

Although the 250 mg/month dosage of fulvestrant is clearly effective, there is an opportunity to test whether its efficacy in the first- and second-line settings can be improved with the use of alternative dosing or combination regimens. Such regimens should increase fulvestrant plasma concentrations or concurrently decrease circulating estradiol levels, respectively, thereby increasing the level of ER downregulation. Whether increasing the fulvestrant dose and/or combination treatment with an AI may also delay the onset of resistance is a research question currently under investigation in clinical trials. The use of the fulvestrant approved and HD regimens as well as the use of fulvestrant in combination with trastuzumab may prove particularly useful for patients with HER-2–positive tumors. However, such treatment strategies should not be used in clinical practice until ongoing trials have proven their superiority over the currently approved dosing regimen. Results from ongoing phase II/III clinical trials evaluating these new dosing and combination regimens are awaited with interest.

Acknowledgments

The author acknowledges Dr. Dawn Batty, from Complete Medical Communications Ltd, who provided medical writing support.

Disclosure of Potential Conflicts of Interest

J.F.R.R. has acted as a consultant for AstraZeneca.

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