Fulvestrant (‘Faslodex’) – a new treatment option for patients progressing on prior endocrine therapy

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Abstract
Since its introduction more than 30 years ago, tamoxifen has been the most widely used endocrine therapy for the treatment of women with advanced breast cancer. More recently, a number of alternative endocrine treatments have been developed, including several selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs) and, most recently, fulvestrant (‘Faslodex’). Fulvestrant is an estrogen receptor (ER) antagonist, which, unlike the SERMs, has no known agonist (estrogenic) effect and downregulates the ER protein. Tamoxifen is effective and well tolerated, although the non-steroidal AIs, anastrozole and letrozole, are more effective treatments for advanced disease than tamoxifen. Fulvestrant has recently gained US Food and Drug Administration approval for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. In two global phase III clinical trials fulvestrant was at least as effective and as equally well tolerated as anastrozole for the treatment of postmenopausal women with advanced and metastatic breast cancer. In a retrospective analysis of the combined data from these trials, mean duration of response was significantly greater for fulvestrant compared with anastrozole. These new hormonal treatments expand the choice of endocrine therapy for women with advanced breast cancer and offer new options for sequencing and combining treatments.

Introduction
Although important for normal physiological growth processes, estrogens are also known to play a significant role in the stimulation and growth of breast tumors (Hulka 1996). Estrogens regulate cell growth and differentiation by binding to specific receptors that are present in 50-80% of breast tumors (Bruneggermeier 2001, Johnston 2001). Inhibition of estrogen production or reducing the binding of estrogen to the estrogen receptor (ER) have long been recognized as rational target mechanisms for the development of therapeutic agents and have been clinically exploited for the treatment of hormone-sensitive breast cancer (Fuqua et al. 1992).

In an attempt to block the effects of estrogen, a number of different hormonal agents have been developed for the treatment of breast cancer. Over the past 60 years, androgens, progesterones and pharmacological doses of estrogens have been used to treat breast malignancies (Goldenberg et al. 1973, Pritchard & Sutherland 1989, Espie 1994). Although these therapies have shown efficacy in some women, they are all poorly tolerated, limiting their acceptance and usage, especially for the treatment of advanced disease where maintaining quality of life is a major objective of treatment (Gill et al. 1993).

Over the past 30 years, tamoxifen, an antiestrogen that competitively inhibits estrogen–ER binding, has been the most widely used endocrine therapy for the treatment of breast cancer (Bazdar 2001). Tamoxifen provides effective palliation in patients with advanced disease and, when used as adjuvant therapy, produces significant increases in both disease-free and overall survival (Fisher et al. 2001). Tamoxifen exhibits both estrogen agonist and antagonist effects, depending on its target tissue. In the breast, tamoxifen acts primarily as an estrogen-antagonist, whereas in bone, liver, and the uterus, it acts predominantly as an estrogen-agonist. The estrogen-agonist properties of tamoxifen can generate positive effects in some tissues: in blood it may help reduce serum cholesterol, and in bone tamoxifen helps to maintain
bone mineral density (Chang et al. 1996, Powles et al. 1996). In other tissues, however, the estrogen-agonist effects of tamoxifen may lead to a number of unwanted side effects such as an increased risk of endometrial cancer (Fisher et al. 1994). Tamoxifen is clearly of significant clinical value and provides an important therapeutic option. However, many patients, particularly those with advanced disease, will experience disease progression and require further treatment options (Wolf et al. 1993).

In the search for improved efficacy over tamoxifen, and for the provision of additional effective hormonal therapy after progression on tamoxifen, a number of new antiestrogenic therapies have been developed. These include several additional non-steroidal agents, collectively termed the selective ER modulators (SERMs), that work in a similar way to tamoxifen (Dhingra 2001), non-steroidal and steroidal aromatase inhibitors (AIs) that inhibit the synthesis of estrogen in postmenopausal women (Miller & Dixon 2000), and most recently, fulvestrant (‘Faslodex’) a new ER antagonist that downregulates cellular levels of the ER (Howell et al. 2000). These new endocrine therapies may offer the opportunity for longer disease control in patients with advanced disease who have progressed on tamoxifen.

Developments in antiestrogen therapy

Selective estrogen receptor modulators

Toremifene (Hayes et al. 1995), raloxifene (Thiebaud & Secrest 2001), idoxifene (Dowsett et al. 2000), and drolxifene (Rauschning & Pritchard 1994) are all antiestrogens that, like tamoxifen, compete with estrogen for the ER and have been collectively termed SERMs. However, none of these agents has demonstrated any therapeutic advantage over tamoxifen. Moreover, due to their similar modes of action, patients who have previously been treated with tamoxifen are likely to have developed cross-resistance to these agents (Lee et al. 2000).

Aromatase inhibitors

Aromatase inhibitors inhibit the enzyme (aromatase) that drives the conversion of adrenal-derived androgen to estrogen in postmenopausal women. Both the third-generation, non-steroidal AIs, anastrozole (‘Arimidex’) and letrozole, have efficacy advantages over tamoxifen in postmenopausal patients as first-line therapy (Bonneteer et al. 2000, Nabholz et al. 2000, Mouridsen et al. 2001). Anastrozole also demonstrates a safety advantage over tamoxifen (Bonneteer et al. 2000). These AIs are more effective than megestrol acetate after progression on tamoxifen (Buzdar et al. 1998, Dombernowsky et al. 1998). Exemestane, a third-generation steroidal AI, has also shown survival benefits over megestrol acetate as second-line therapy (Kaufmann et al. 2000). In the light of the improved response rates produced by anastrozole and letrozole compared with tamoxifen, AIs are now becoming the agents of choice for first-line treatment of advanced breast cancer in postmenopausal women, relegating tamoxifen to a second- or possibly even third-line treatment option.

Recently, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial has compared anastrozole with tamoxifen in postmenopausal women with early breast cancer. Currently available data from over 9300 patients suggests superiority of anastrozole over tamoxifen in terms of improved disease-free survival. Anastrozole alone was significantly more effective than the combination of anastrozole and tamoxifen (The ATAC Trialists’ Group 2002).

Fulvestrant: preclinical data

Estrogen receptor downregulation

Fulvestrant is the first of a new type of ER antagonist that has no known agonist effects and that downregulates cellular levels of the ER protein (Wakeling 2000). Like tamoxifen, fulvestrant competitively binds to the ER but with a much greater affinity than tamoxifen – approximately 89% that of estradiol, compared with 2.5% for tamoxifen (Wakeling & Bowler 1987, Wakeling et al. 1991). Unlike tamoxifen, fulvestrant causes complete abrogation of estrogen-sensitive gene transcription and therefore does not exhibit the agonist effects commonly associated with SERMs (Wakeling 2000).

Fulvestrant also exerts a number of additional effects on the ER that give rise to a more effective inhibition of the action of estrogen on breast tissue. These include inhibition of ER dimerization (Fawell et al. 1990), and reduced shuttling of the ER from the cytoplasm to the nucleus (Dauvois et al. 1993). The fulvestrant–ER complex is also thought to be highly labile, leading to its rapid degradation and hence a marked loss of cellular ER (Fawell et al. 1990). A schematic diagram highlighting the different approaches to antiestrogen therapy, AIs, SERMs and fulvestrant, is shown in Fig. 1.

Pharmacology of fulvestrant

Studies in immature female rats demonstrated that, unlike tamoxifen, fulvestrant had no uterotrophic (estrogen-agonist) activity; when fulvestrant was co-administered with estradiol or tamoxifen, it effectively blocked the uterotrophic activity of both of these agents in a dose-dependent and complete manner. In pigtailed monkeys, sustained antiestrogenic effects were apparent following a single parenteral dose of fulvestrant (Wakeling et al. 1991). Further observations from this study showed that the oral antiuterotrophic activity of fulvestrant was one order of magnitude less than its parenteral potency (Wakeling et al. 1991).

Further characterization of fulvestrant was conducted in ovariectomized adult female monkeys in order to provide an
Figure 1 Three different approaches to hormonal therapy for breast cancer. (a) SERMs (S) compete with estrogen (E) for binding to the ER and inhibit the transcription of estrogen-sensitive genes to a greater or lesser degree depending on the target tissue. (b) Aromatase inhibitors (AIs) compete with androgen for the aromatase enzyme binding site, preventing the conversion of androgen to estrogen in postmenopausal women. (c) Fulvestrant (F) competitively inhibits the binding of estrogen (E) to the ER, prevents dimerization, promotes ER degradation and prevents transcription of estrogen-sensitive genes. ERE, estrogen response element.

indication of its potential actions in postmenopausal women. Single intramuscular (i.m.) injections of fulvestrant produced sustained blockade of estradiol action on the monkey uterus in a dose-dependent manner for 3–6 weeks. Repeated injections of 4 mg/kg fulvestrant at 4-week intervals provided increasingly effective blockade of uterine proliferation. Fulvestrant also produced involution of the uterus, similar to that seen following estrogen withdrawal (Dukes et al. 1992).
The antitumor activity of fulvestrant was first demonstrated in two models of human breast cancer grown in nude mice; the growth of xenografts of MCF-7 cells, supported by continuous treatment with estradiol, was completely blocked for at least 4 weeks following a single injection of 5 mg fulvestrant. Similar reductions of tumor growth were seen in the Br10 human tumor model (Wakeling et al. 1991).

Additional studies in nude mice carrying xenografts of MCF-7 cells showed that fulvestrant suppressed the growth of established tumors for twice as long as treatment with tamoxifen. Tumor growth was also delayed to a greater extent in fulvestrant-treated mice than in tamoxifen-treated mice. Tamoxifen-resistant breast tumors, which grew in nude mice after long-term tamoxifen treatment, remained sensitive to growth inhibition by fulvestrant, indicating that fulvestrant is likely to be effective in patients with acquired resistance to tamoxifen. Fulvestrant was also more effective than tamoxifen in reducing the expression of ER and progesterone receptor (PgR) (Osborne et al. 1994, 1995).

**Human pharmacokinetics and biological effects**

In one study, pharmacokinetic analyses of two dose regimens of fulvestrant (250 mg) indicated that there was no significant difference in the area under the concentration–time curve (AUC) between a single 5 ml dose and 2 × 2.5 ml doses; plasma concentration at 28 days (C_{min}) and the maximum plasma fulvestrant concentration (C_{max}) were also similar between the two groups. Plasma concentration–time profiles and overall exposure to fulvestrant were similar for both dose regimens. The ratio of geometric means of AUC_{0–28} for the two regimens was 1.01; 95% confidence interval (CI) 0.68 to 1.51) showed there was no difference between the treatment regimens (P = 0.94) (Robertson 2000). When given monthly, fulvestrant plasma concentration profiles were similar for the two dose regimens, reaching steady state after 3–6 doses. Comparison with single-dose data showed approximately a twofold accumulation. In another study, both regimens of fulvestrant were equally effective in maintaining plasma fulvestrant levels for at least 30 months (Erikstein et al. 2001).

Over the past decade, the biological effects of fulvestrant have been evaluated in trials in postmenopausal women with primary breast cancer. In a phase I/II trial, 56 postmenopausal women with primary breast cancer were randomized to treatment with seven daily doses of 6 mg or 18 mg of a short-acting formulation of fulvestrant contained in a propylene glycol-based vehicle, or observation. Serum concentrations of fulvestrant were found to be dose dependent and a threefold accumulation of the drug occurred over the 7-day period. A significant decrease in expression of ER and PgR provided evidence of both ER downregulation and of the absence of an estrogen-like effect. Reduced tumor cell proliferation, indicated by reduced Ki67 expression and reduced expression of the estrogen-regulated protein pS2, was also observed (DeFriend et al. 1994).

In a subsequent study, previously untreated postmenopausal women with primary breast cancer were randomized to the following: a single i.m. injection of sustained-release fulvestrant 50, 125, or 250 mg, continuous oral daily tamoxifen, or matching placebo for 14–21 days before surgery with curative intent. Analyses of post-surgical specimens showed statistically significant reductions in ER expression at all doses of fulvestrant compared with placebo, and for fulvestrant 250 mg compared with tamoxifen (Fig. 2). Fulvestrant produced significant dose-dependent reductions in Ki67 compared with placebo, although there were no significant differences in Ki67 labeling between fulvestrant and tamoxifen. For PgR expression, fulvestrant produced significant reductions at the 125 mg and 250 mg doses compared with placebo. In contrast, tamoxifen produced a significant increase in PgR expression relative to placebo, a finding that can be attributed to its partial agonist effects and confirming that fulvestrant has a different mode of action to tamoxifen (Robertson et al. 2001). In an analysis of the single-dose pharmacokinetics from this trial, C_{max}, C_{min}, and AUC increased proportionally with all doses of fulvestrant. The ER index was reduced by 32, 55, and 72% for 50, 125, and 250 mg fulvestrant respectively, indicating a dose–response relationship with respect to ER downregulation (Robertson et al. 2000). Given the time to steady state, there may be a delay in attainment of maximal ER downregulation, and further clinical trials are planned to investigate whether use of a loading dose of fulvestrant may shorten the time to steady state, thereby improving the potential for response.

**Clinical efficacy in postmenopausal women with tamoxifen-resistant advanced breast cancer**

**Phase I/II trials**

Initial efficacy data for fulvestrant in postmenopausal patients with tamoxifen-resistant advanced breast cancer showed a clinical benefit (CB) (complete response + partial response + stable disease for a duration of ≥ 24 weeks) 69% with a median duration of response (DoR) of 26 months (Howell et al. 1996). As predicted from preclinical data, these findings demonstrated that fulvestrant was not cross-resistant with tamoxifen in the clinical setting.

**Phase III trials**

Two phase III trials (0020 and 0021) were conducted to establish the efficacy of fulvestrant for the treatment of postmenopausal women with advanced disease after progression on prior endocrine therapy (Howell et al. 2002, Osborne
The trials were prospectively designed to allow combination of results. Anastrozole, the first of the new generation of non-steroidal AIs to gain US Food and Drug Administration (FDA) approval for the second-line treatment of advanced breast cancer in postmenopausal women progressing on tamoxifen, was chosen as the comparator in these trials. Both trials compared fulvestrant (250 mg/i.m., once/monthly) with anastrozole (1 mg/orally, once/daily).

Trial 0020 was a randomized, open-label trial conducted in Europe, South Africa and Australia in which fulvestrant was given as a 1×5 ml i.m. injection. In this trial, the objective response (OR) rate was similar for fulvestrant and anastrozole (20.7% vs 15.7% respectively; P = 0.20). Median time to progression (TTP), the primary endpoint, was 5.5 months for fulvestrant and 5.1 months for anastrozole (Hazard ratio (HR) 0.98; 95% CI 0.80 to 1.21; P = 0.84) (Fig. 3a) and after an extended median follow-up of 22.6 months, median DoR was 15.0 months for fulvestrant and 14.5 months for anastrozole (Fig. 4a) (Howell et al. 2002).

Trial 0021 was a double-blind, double-dummy study conducted in North America in which patients were given fulvestrant as 2×2.5 ml i.m. injections. The OR rate was similar in both treatment arms (17.5%; P = 0.96). However, the CB rate was higher for fulvestrant compared with anastrozole (although this was not statistically significant) (42.2% vs 36.1% respectively; 95% CI -4.00% to 16.41%, P = 0.26). Median TTP was 5.4 months for fulvestrant and 3.4 months for anastrozole (HR 0.92; 95.14% CI 0.74 to 1.14; P = 0.43) (Fig. 3b). In responding patients, an extended median follow-up of 21.3 months, median DoR was 19.0 months for fulvestrant and 10.8 months for anastrozole (Fig. 4b) (Osborne et al. 2002).

The Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire (Cella et al. 1993) is a sensitive measure for evaluating physical, functional, social and emotional well-being of the patient. Using the FACT-B questionnaire, both phase III trials demonstrated that quality of life (QoL) during treatment with fulvestrant was similar to that during treatment with anastrozole. Fulvestrant and anastrozole were equally well tolerated with a similar number of adverse events (AEs) in both treatment groups (Howell et al. 2002, Osborne et al. 2002).

Fulvestrant may offer certain benefits compared with daily oral dosing regimens. As the injection is given monthly, patients do not have to remember to take tablets between clinic visits, which may offer enhanced patient compliance when compared with oral administration.

**Combined analyses of phase III trials**

After a median follow-up of 15.1 months, analyses of the combined data from both trials showed median TTP of 5.5 months and 4.1 months (HR 0.95; 95% CI 0.82 to 1.10; P = 0.48) and OR rates of 19.2% and 16.5% for fulvestrant and anastrozole respectively. Overall treatment effect was significant (P < 0.0003). The trials were prospectively designed to allow combination of results. Anastrozole, the first of the new generation of non-steroidal AIs to gain US FDA approval for the second-line treatment of advanced breast cancer in postmenopausal women progressing on tamoxifen, was chosen as the comparator in these trials. Both trials compared fulvestrant (250 mg/i.m., once/monthly) with anastrozole (1 mg/orally, once/daily).

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anastrozole respectively (odds ratio 1.21; 95% CI 0.84 to 1.74; \( P = 0.31 \)) (Howell et al. 2001). An updated efficacy analysis from an extended median follow-up of 22.1 months produced a median DoR, from randomization to progression in responding patients, of 16.7 months for fulvestrant and 13.7 months for anastrozole. In a new analysis of DoR that included all randomized patients rather than only those that responded to treatment, mean DoR (defined for responders as the onset of response to disease progression, and for non-responders as zero) was significantly (30%) greater for fulvestrant than for anastrozole (ratio of average response durations = 1.30; 95% CI 1.13 to 1.50; \( P > 0.01 \)) (Parker & Webster 2002).

In the analysis of AEs, 46.1% of patients treated with fulvestrant and 40.4% of those treated with anastrozole reported drug-related AEs. Seven AEs commonly associated with endocrine therapy were predefined for statistical analysis; there was no significant difference between fulvestrant and anastrozole for the proportion of patients reporting gastrointestinal disturbances (46.3% vs 43.7%), hot flashes (21.0% vs 20.6%), urinary tract infection (7.3% vs 4.3%), thromboembolic disease (3.5% vs 4.0%), vaginitis (2.6% vs 1.9%) and weight gain (0.9% vs 1.7%). However, the incidence of joint disorders was significantly lower with fulvestrant compared with anastrozole (5.4% vs 10.6% \( P = 0.0036 \)) (Howell et al. 2001).

In a subgroup analysis of 381 patients, both drugs showed efficacy in patients with visceral metastases; 38.2% of patients treated with fulvestrant and 37.4% treated with anastrozole achieved CB, and 15.7% of patients treated with
fulvestrant and 13.2% treated with anastrozole achieved an OR. These data indicate that patients with visceral metastases derived a similar benefit from endocrine therapy to those without visceral metastases (CB 47.6% vs 43.8%; OR 21.9% vs 19.3% for fulvestrant and anastrozole respectively) (Mauriac et al. 2002).

**Fulvestrant: future perspectives**

In April 2002, fulvestrant gained FDA approval for the treatment of postmenopausal women with hormone-sensitive advanced or metastatic breast cancer who have progressed on prior antiestrogen therapy. This new hormonal therapy will provide a valuable option for the treatment of hormone-sensitive disease.

In a recently reported phase III trial comparing fulvestrant with tamoxifen for first-line treatment of advanced breast cancer, median TTP was not significantly different between the groups (median TTP for fulvestrant and tamoxifen: 6.8 months vs 8.3 months; HR 1.18; 95% CI 0.98 to 1.44; \( P = 0.088 \)). Rates of OR (fulvestrant 31.6% and tamoxifen 33.9%; \( P = 0.451 \)) were also similar between the two treatment groups. In a prospectively defined subgroup of ER-positive and/or PgR-positive tumors, median TTP was 8.2 months.

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**Figure 4** Kaplan-Meier estimates for duration of response (DOR; all patients) from onset of response to disease progression in (a) trial 0020 and (b) trial 0021. (Reprinted by permission of Howell et al. 2002)
months for fulvestrant and 8.3 months for tamoxifen (HR 1.10; 95% CI 0.89 to 1.36; \( P = 0.388 \)) and OR was 33.2% with fulvestrant and 31.1% with tamoxifen (Robertson et al. 2002). In a retrospective subgroup of patients with both ER-positive and PgR-positive tumors, TTP was 11.4 months for fulvestrant and 8.5 months for tamoxifen (HR 0.85; 95% CI, 0.63 to 1.15). In this subgroup, OR rates favored fulvestrant over tamoxifen (44.3% vs 29.8% respectively; \( P = 0.019 \)). These data demonstrate that fulvestrant is effective and well tolerated in the first-line setting; further investigation may be required to better characterize the most appropriate first-line population in which fulvestrant should be used.

The development of agents that are more effective than tamoxifen in the treatment of postmenopausal women with advanced breast cancer, may mean that tamoxifen will be used as a later treatment option. At the same time, the use of AIs as first-line therapy looks set to change the sequence of hormonal therapy for advanced disease, which necessitates re-assessment of the choice of second- and third-line therapies. In a retrospective analysis of 57 women with advanced breast cancer who had progressed after achieving a CB on fulvestrant subsequent to response and progression on tamoxifen, third-line hormonal therapy with anastrozole and letrozole produced CB in approximately 47% of patients (Vergote 2002). Interestingly, responses were seen in patients who had derived CB from fulvestrant treatment and also in those who had not. This suggests that patients who progress on fulvestrant retain sensitivity to subsequent hormonal therapy. Investigations into the efficacy of fulvestrant after AIs are now essential and studies are underway to assess this; preliminary data have shown responses to fulvestrant in postmenopausal patients who had previously been treated with AIs after progression on tamoxifen (Perey et al. 2002).

Combinations of antiestrogen therapy with other anti proliferative agents may prove to be effective in enhancing efficacy in the treatment of advanced breast cancer. Recent preclinical studies have demonstrated that breast cancer cell lines that have developed resistance to fulvestrant show an increased dependence on epidermal growth factor receptor (EGFR)-mediated signaling (McClelland et al. 2001). These cells are highly sensitive to growth inhibition by the EGFR-tyrosine kinase inhibitor (EGFR-TKI) gefitinib (‘Iressa’ ZD1839), an effective inhibitor of cell proliferation (Chan et al. 2001). The combination of fulvestrant with other therapies with different modes of action, such as gefitinib, may thus provide future possibilities for enhancing response rates in breast cancer therapy.

Fulvestrant is an effective treatment option for postmenopausal women with advanced or metastatic breast cancer who have progressed on prior endocrine therapy. As fulvestrant is not cross-resistant with other endocrine agents it may prolong the time in which treatment with well-tolerated hormonal therapy is possible, thus delaying the need for cytotoxic chemotherapy. Fulvestrant will therefore be a valuable additional therapy to currently available options for women with advanced breast cancer.

References


Morris and Wakeling: Fulvestrant


Robertson JFR 2000 A comparison of the single-dose pharmacokinetics of ICI 182,780 (‘Faslodex’) 250 mg when given as either a one × 5-ml intramuscular injection or two × 2.5-ml injections in postmenopausal women with advanced breast cancer. *Breast Cancer Research and Treatment* 64 53 (abstract 172).


