Drugs 2001; 61 (6): 807-813
0012-6667/01/0006-0807/$27.50/0

Fulvestrant

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Contents

Abstract

▲ Fulvestrant is a 7α-alkylsulphinyl analogue of estradiol that competes with endogenous estrogen for binding to the estrogen receptor. Once bound to the receptor, fulvestrant attenuates receptor dimerisation, effecting a rapid degradation of the estrogen receptor protein and inhibition of transcription.

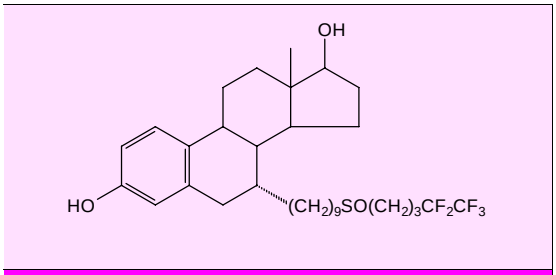
▲ Fulvestrant is a potent inhibitor of the growth of human breast cancer cells *in vitro* and *in vivo*. It has demonstrated pure anti-estrogenic activity in animal systems.

▲ Intramuscular fulvestrant 250mg once a month was as effective as the oral aromatase inhibitor anastrozole 1 mg/day in 2 phase III trials in postmenopausal women with advanced breast cancer who had received prior endocrine therapy.

▲ Median time to disease progression (the primary end-point) with fulvestrant and anastrozole was 5.4 and 3.4 months (North American trial) and 5.5 and 5.1 months (European trial). The median duration of response was 19.3 and 10.5 months (North American trial) and 14.3 and 14.0 months (European trial).

▲ The most common adverse events with fulvestrant are gastrointestinal disturbances and hot flushes. Fulvestrant showed similar tolerability to anastrozole in 2 phase III trials.

Features and properties of fulvestrant	
Indications	
Advanced breast cancer in postmenopausal women	
Mechanism of action	
Antineoplastic agent	A steroidal antiestrogen that competes with estrogen for binding to the estrogen receptor. Binding of fulvestrant to the receptor attenuated its dimerisation, resulting in degradation of the receptor and inhibition of transcription.
Dosage and administration	
Usual dosage in clinical trials	250mg
Route of administration	Intramuscular
Frequency of administration	Once monthly
Pharmacokinetic profile (multiple-dose 250mg once monthly: value at 6 months)	
Peak plasma concentration	12.8 μg/L
Time to peak plasma concentration	7 days
Area under the plasma concentration-time curve	206.8 μg/L • day
Adverse events	
Most frequent	Gastrointestinal disturbances, hot flushes



Fulvestrant

The anti-estrogen tamoxifen is currently the most widely used endocrine therapy for postmenopausal breast cancer. Tamoxifen acts as both an estrogen antagonist and a partial estrogen agonist. Thus, recent research has focused on finding an agent which has only estrogen antagonist activity. Fulvestrant is a steroidal analogue of estradiol (alkylsulphinyl substituent group at the 7α position) that has shown high affinity for the estrogen receptor and estrogen antagonist activity. Consequently, it is being investigated in the treatment of postmenopausal advanced breast cancer.

1. Pharmacodynamics

Mechanism of Action

• Fulvestrant exerts its antitumour activity by competing with endogenous estrogen for binding to the estrogen receptor. The relative binding affinity of fulvestrant for the estrogen receptor was 89% that of estradiol,[1] whereas that of tamoxifen was 2.5%.[2]

• Binding of fulvestrant to the estrogen receptor appears to prevent receptor dimerisation; consequently, the binding of the receptor complex to estrogen response elements is prevented and transcription is not activated.[3] It has been suggested that the receptor complex formed with fulvestrant is fragile and sensitive to degradation.[4] This explanation could account for the reduced level of estrogen receptor, with no change in mRNA levels, seen in both human breast cancer cells and mouse uterine studies.[5,6] In addition, it has been suggested that fulvestrant may reduce the shuttling of the estrogen receptor from the cytoplasm to the nucleus, thus promoting its degradation.[7]

Antitumour Activity *In Vitro* and *In Vivo*

• Fulvestrant displays *in vitro* inhibitory activity against estrogen-responsive human breast cancer cells including those from the MCF-7 and T47D cell lines.[1,8-10] Concentrations of fulvestrant as low as 14 nmol/L have been shown to inhibit the proliferation of MCF-7 cells by 50% (IC_{50}). Tamoxifen is a less potent inhibitor of MCF-7 cell growth, with IC_{50} values of 2 μmol/L.[9,11]

• Fulvestrant delays tumorigenesis and suppresses growth of established tumours in animal models of breast cancer.[1,12] In nude mice bearing established MCF-7 xenografts, the median time to tumour progression (after estrogen removal) was 200 days in animals treated with fulvestrant, nearly twice as long as that in animals given tamoxifen (104 days) or in those undergoing estrogen withdrawal alone (97 days).[12] MCF-7 tumorigenesis (in the absence of supplemental estrogen) was significantly delayed by fulvestrant compared with tamoxifen; tumours developed after 2 months in tamoxifen-treated mice, while in fulvestrant-treated mice, tumours grew very slowly or not at all, with barely measurable tumours present at day 70.[12] A single subcutaneous injection of fulvestrant 5mg and oral tamoxifen 10 mg/kg/day inhibited the growth of estradiol-dependant MCF-7 xenografts in nude mice to a similar extent (for at least 1 month).[1]

• The antitumour activity of fulvestrant has been demonstrated in *in vitro* and *in vivo* models of tamoxifen-resistant breast cancer.[9,13,14] In a tamoxifen-resistant variant of the parental MCF-7 human breast cancer cell line, fulvestrant completely inhibited cell growth at concentrations of 5 to 10 nmol/L.[13] Fulvestrant prevented the growth of tamoxifen-resistant MCF-7 tumours in mice.[14] Fulvestrant also demonstrated anticlonogenic activity in tumour cells obtained from breast cancer patients who had relapsed during tamoxifen treatment.[15]

• Fulvestrant was more effective than 4-hydroxytamoxifen in inhibiting insulin-like growth factor-1 (IGF-1)-stimulated cellular proliferation in estrogen-receptor-positive cell lines.[8] The attenuation of IGF responsivity observed in MCF-7 human breast cancer cells treated with fulvestrant may in part be due to the reduction of IGF receptor expression by fulvestrant.[16]

• Fulvestrant inhibits cellular aromatase activity in fibroblasts isolated from the normal human breast and in carcinoma cell lines (MCF-7Ca breast cancer and JEG-3 choriocarcinoma).[17] IC_{50} values were 16.8 nmol/L in MCF-7Ca cells, 125.5 nmol/L in JEG-3 cells and 386.1 nmol/L in breast fibroblasts.

• Fulvestrant-resistant MCF-7 colonies were isolated after 22 days' treatment with fulvestrant 10 μmol/L. The fulvestrant-sublines showed cross-resistance to the anti-estrogen ICI 164384; however, they were not resistant to tamoxifen, with a similar sensitivity to that seen in the parent cell line.[11]

Effects on Estrogen-Responsive Organs and Tissues

• Fulvestrant appears to have pure anti-estrogenic activity. In the rat uterus, it displayed no uterotrophic activity and blocked the uterine stimulatory effects of estradiol and tamoxifen.[1] Similarly, fulvestrant demonstrated an anti-uterotrophic effect in female monkeys, as determined by endometrial and myometrial volume changes.[18]

• The effect of fulvestrant on bone mineral density is equivocal. A reduction of ≈30% in bone volume at the tibial metaphysis was noted after fulvestrant treatment in rats.[19] Fulvestrant also inhibited 17β-estradiol-stimulated calcium absorption in cultured fetal mouse parietal bones.[20] In contrast, bone mineral density in rats was not altered by administration of fulvestrant at anti-uterotrophic doses, unlike the significant reduction that occurred after an ovariectomy.[21]

Endocrine and Lipid Effects in Clinical Studies

• An early phase I clinical study in 56 menopausal women with estrogen-responsive breast cancer has shown that fulvestrant 6 or 18 mg/day for 7 days prior to primary breast surgery promoted dose-dependent decreases in tumour expression of the estrogen receptor (median estrogen receptor index 0.72 before *vs* 0.02 after treatment; $p < 0.001$), the progesterone receptor (median progesterone receptor index 0.50 *vs* 0.01; $p < 0.05$) and the tumour cell proliferation marker Ki67 (median Ki67 labelling index, 3.2 *vs* 1.1; $p < 0.05$).[22] Fulvestrant also significantly reduced pS2 expression ($p < 0.05$), but this appeared unrelated to tumour estrogen receptor status. Fulvestrant had no effect on serum gonadotropin or sex hormone-binding globulin levels.

• In a multicentre, randomised, partially-blinded trial (data presented as an abstract),[23] in which postmenopausal women with breast cancer received fulvestrant 50, 125, or 250 mg/day for 14 to 21 days prior to tumour resection, the dose-dependent reduction in estrogen receptor protein was shown to be significantly different from that of tamoxifen 20 mg/day for the highest fulvestrant dosage. The dose-dependent reduction in progesterone receptor index was significantly different from that of tamoxifen for all fulvestrant dosages.

• In 19 women with advanced breast cancer resistant to tamoxifen, treatment with fulvestrant 250 mg/month for 6 months did not significantly affect serum prolactin, sex hormone-binding globulin or lipid levels.[24] Luteinising hormone and follicle-stimulating hormone levels were below the normal range at baseline, possibly related to previous tamoxifen therapy. During the first 3 months of the study, these levels increased but reached a plateaux for the remainder of the study. Serial ultrasound measurements of the uterus to determine endometrial thickness were performed in 5 of the patients. These patients had endometrial thickening that was compatible with the partial agonistic effect of previous tamoxifen therapy. Notably, there was no

change in endometrial thickness during up to 15 months' therapy with fulvestrant.

• There was no change in endometrial thickness and no ultrasonic evidence of ovarian hyperstimulation in premenopausal women treated with fulvestrant 12 mg/day for 7 days before undergoing hysterectomy.[25]

2. Pharmacokinetic Profile

The pharmacokinetic properties of single doses of intramuscular fulvestrant were assessed in 2 multicentre, randomised trials (data presented as abstracts) in postmenopausal women with advanced[26] or primary breast cancer.[27] In addition, the pharmacokinetics of multiple-dose fulvestrant administration in patients with advanced breast cancer were assessed in a phase II trial[24] and in a subset of patients enrolled in a phase III trial (data presented as an abstract).[28]

• Dose-proportional pharmacokinetics occurred when single-dose fulvestrant was administered to previously untreated postmenopausal women with primary breast cancer (n = 58).[27] After administration of fulvestrant 50, 125 or 250mg, mean maximum plasma concentration (C_{max}) values were 2.0, 4.3 and 7.4 μg/L and mean areas under the plasma concentration-time curve (AUC) after 28 days were 32.9, 69.1 and 116.5 μg/L · day. In a phase II study,[24] C_{max} values were reached after a median 8 to 9 days; then drug plasma concentrations declined, but remained within the estimated therapeutic range after 28 days.

• Trough fulvestrant plasma concentrations (i.e. at the end of the month) were 5.6 versus 3.1 μg/L, and AUC values were 206.8 versus 140.5 μg/L · day after the sixth compared with the first month of fulvestrant 250 mg/month,[24] suggesting drug accumulation after multiple dose administration. Similarly, in another long term study in which patients received fulvestrant for up to 21 months, mean trough concentrations were 6.1 versus 2.8 μg/L, and AUC values increased 2.3-fold, after the sixth compared with the first month of administration.[28]

• The administration regimen did not alter the pharmacokinetic profile of fulvestrant. Administration of fulvestrant 250mg as either one 5ml or two 2.5ml injections in postmenopausal women with advanced breast cancer resulted in mean AUC values of 106.8 and 105.5 μg/L · day.[26] Fulvestrant plasma concentrations at 28 days, C_{max} and median time to C_{max} values were also similar with the 2 regimens.

3. Clinical Trials

Fulvestrant has been investigated as second-line treatment in postmenopausal women with advanced breast cancer that had progressed during or recurred after prior endocrine treatment for early or advanced disease.

Two multicentre, randomised, parallel group phase III trials compared the efficacy of intramuscular fulvestrant 250mg once monthly with that of the aromatase inhibitor anastrozole 1mg administered orally once daily.[29,30] A double-blind study including 400 patients was conducted in North America,[29] and a nonblind study in 451 patients was conducted in primarily in Europe with sites in South Africa and Australia.[30] The primary endpoint in both studies was the time to disease progression, with secondary end-points including objective response (complete and partial response) rates, and duration of response.

In a noncomparative phase II trial, 19 patients received intramuscular fulvestrant 250 mg/month.[31] The patients had relapsed after receiving tamoxifen for advanced breast cancer or after receiving tamoxifen as adjuvant therapy for >2 years. Response to treatment was evaluated according to International Union Against Cancer (UICC) criteria.

• The median time to disease progression was longer with fulvestrant compared with anastrozole administration in the North American (5.4 *vs* 3.4 months) and in the European trial (5.5 *vs* 5.1 months); however, the difference was not statistically significant in either trial. Median duration of response was longer with fulvestrant compared with anastrozole administration in the North Amer-

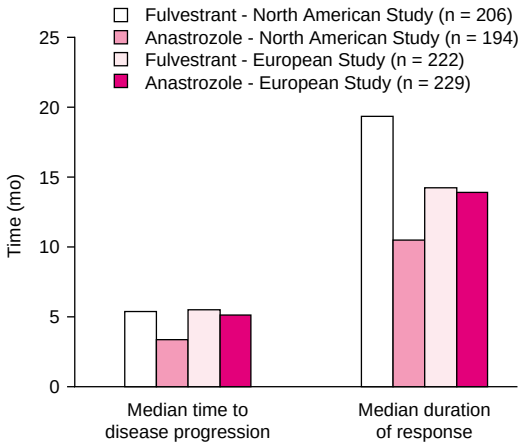


Fig. 1. Clinical efficacy of intramuscular fulvestrant 250 mg/month and oral anastrozole 1 mg/day in 2 phase III studies in postmenopausal women with advanced breast cancer.[29,30]

ican trial (19.3 *vs* 10.5 months) and in the European trial (14.3 *vs* 14.0 months); however, statistical analyses were not performed (fig. 1).

- In the North American phase III study, the objective response rates were the same in fulvestrant and anastrozole recipients (17.5%). Clinical benefit rates (defined as complete and partial response and disease stabilisation lasting ≥24 weeks) were 42.2 and 36.1%, respectively. In the European trial, the objective response was not significantly higher in fulvestrant than in anastrozole recipients (20.7 *vs* 15.7%). The clinical benefit rate was 44.5 versus 45.0%.

- In a phase II trial in patients with tamoxifen-resistant breast cancer, 7 (37%) patients had a partial response to therapy and 6 (32%) patients had stable disease for a median duration of >18 months. A study that compared this group of patients with megastrol acetate-treated patients with similar clinical characteristics reported the duration to be 26 months.[32] After 16 to 23 months, 9 patients had a partial response or stable disease and were continuing therapy with fulvestrant.[31]

4. Tolerability

- The most frequently reported adverse events observed with fulvestrant were gastrointestinal disturbances (incidence of 40% in the European study and 53% in the North American trial) and hot flushes (19 and 24%).[29,30] In addition, weight gain (1 and 2%), and vaginitis (2 and 3%) were also reported in the European and North American trials, respectively.

- The incidence of adverse events was similar in fulvestrant and anastrozole recipients in both phase III trials (fig. 2).[29,30] The withdrawal rates in the fulvestrant and anastrozole treatment groups were both low, with 3.2 versus 2.2% of patients withdrawing in the European study[30] and 2.5 versus 2.6% of patients withdrawing in the North American study (statistical significance not stated).[29]

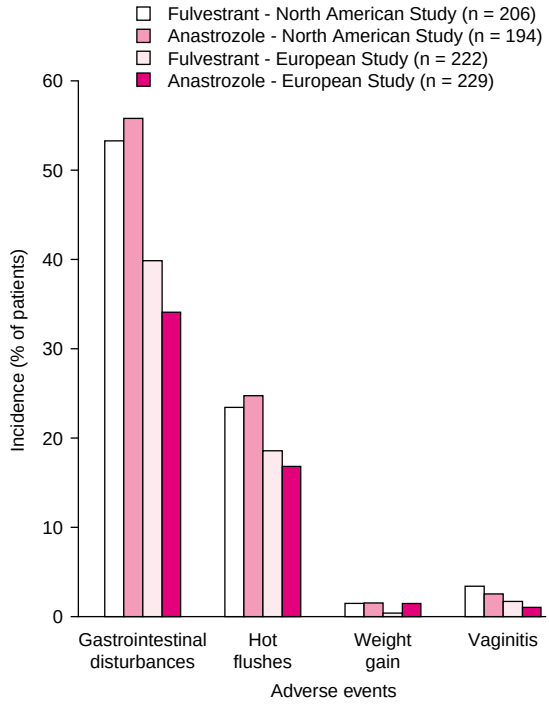


Fig. 2. Tolerability profile of intramuscular fulvestrant 250 mg/ month and oral anastrozole 1 mg/day in 2 phase III studies in postmenopausal women with advanced breast cancer.[29,30]

5. Current Status

Fulvestrant is a pure anti-estrogen that has shown efficacy as second-line therapy in postmenopausal women with advanced breast cancer. Clinical trials have found the drug to compare favourably with anastrozole in terms of clinical efficacy and tolerability in this patient group. Ongoing trials are investigating fulvestrant as first-line therapy for advanced breast cancer and in the neoadjuvant and premenopausal treatment settings.

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