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REVIEW

The Treatment of Advanced Breast Cancer: Focus on Fulvestrant

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Abstract: Fulvestrant (Faslodex®) is an estrogen receptor antagonist with no agonist effects that competitively binds to the estrogen receptor with greater affinity than tamoxifen. A systematic review was performed to understand the pharmacology and to examine the evidence supporting the clinical use of fulvestrant in the first-line and second-line settings in the treatment of advanced breast cancer. MEDLINE, American Society of Clinical Oncology proceedings, San Antonio Breast Cancer Symposia proceedings, and National Cancer Institute Clinical Trials were searched through October 2009 for trial reports. Data regarding tolerability and patient preference was also collected. Fulvestrant is currently being used in the second or third-line setting, and has similar efficacy to tamoxifen, non-steroidal and steroidal aromatase inhibitors based on clinical data. Though non-inferiority to tamoxifen in the first-line setting was not demonstrated in the overall population, clinical outcomes were similar in most settings. The incidence of adverse effects was low and quality of life assessments demonstrate excellent tolerability.

Keywords: fulvestrant, advanced breast cancer, neoadjuvant, first-line, second-line

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Introduction

Breast cancer is the most common cancer in the United States and the second most common cause of cancer-related death in women.[1] Advances in the early detection of breast cancer with widespread screening have improved stage of detection and overall survival rates, but most women will require some adjuvant therapy in addition to surgical excision.[2,3] Though multiple factors including stage and age must be considered in the selection of adjuvant treatment for women with breast cancer, few are more important than the expression of the estrogen (ER) or progesterone receptor (PR). Patients with cancers that express these hormonal receptors tend to be amenable to treatment with agents such as selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and sulfatase inhibitors.

The National Surgical Adjuvant Breast and Bowel Project P-1 Study (NSABP-1) trial was among the first to demonstrate a role for endocrine therapy in the prevention of recurrence in breast cancer patients.[4] Tamoxifen, a weak ER agonist which by virtue of competitive inhibition of more potent estrogens acts as an antagonist, is the most widely used SERM in the treatment of breast cancer. Though both disease-free and overall survival were improved with tamoxifen use in the ER positive population, side effects including the development of venous thromboembolism, cataracts, and endometrial cancer led to the development of alternate therapies including AIs, which block the conversion of androgens to estrogens in peripheral tissues, and more recently sulfatase inhibitors, which block the conversion of biologically inert estrone sulfate to low potency estrone. The ability of these agents to demonstrate efficacy even after progression with a single anti-estrogenic agent suggests that parallel estrogen pathways exist that may compensate for partial or complete inhibition of one pathway.[5,6]

Fulvestrant is a selective estrogen receptor degrader (SERD), an ER antagonist with no agonist effects that has shown efficacy after the development of resistance to other agents. We review the pharmacology, safety profile, and clinical efficacy of fulvestrant in the treatment of advanced breast cancer.

Mechanism of Action, Metabolism, Pharmacokinetic Profile, and Dosing

Fulvestrant, the long acting form of ICI 182,780, competitively inhibits ER activation and induces down-regulation of functional ER. It has no known agonist properties. Its mechanism of action is based on its steroid structure, which is similar to estradiol with the exception of a long alkylsulphinyl side chain added in the 7α position (Fig. 1). This allows fulvestrant to have a similar affinity for the ER as estradiol and to competitively inhibit the binding of estradiol to ER.[7] By comparison, tamoxifen binds to the ER with 2% of the affinity of estradiol.

Understanding the mechanism of action of fulvestrant at the molecular level is facilitated by understanding the mechanism of action of estradiol. When estradiol binds to the ER, the following events occur: 1) Dissociation of heat shock proteins, 2) ER dimerization, 3) Localization of the estradiol-ER complex to the nucleus and binding to DNA sequences called estrogen response elements (ERE) in the regulatory section of target genes, 4) Recruitment of other transcription factors by the ER activation domains AF1 and AF2.[7]

Fulvestrant antagonizes the estrogen receptor via several methods. Upon binding to the ER, it impairs receptor dimerization and subsequent shuttling of the complex to the nucleus.[8,9] Fulvestrant also inactivates

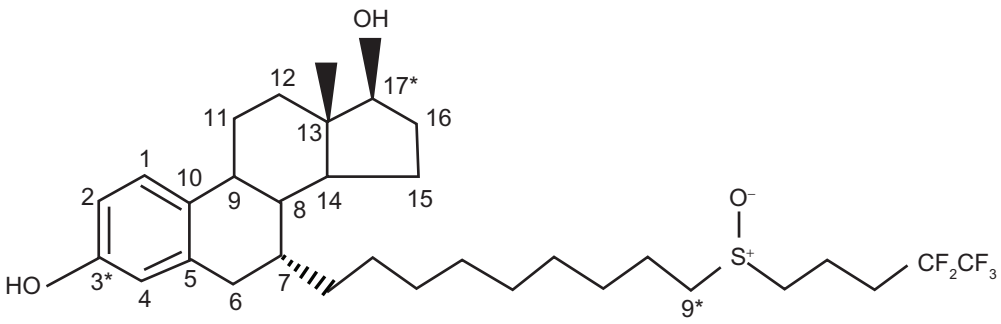

Figure 1. Chemical structure of fulvestrant (From Robertson et al. Fulvestrant: pharmacokinetics and pharmacology).
*Points of metabolism.

AF1 and AF2, so that any fulvestrant-ER complex that does arrive in the nucleus cannot activate transcription. Finally, the fulvestrant-ER complex is unstable resulting in accelerated degradation of ER proteins. These events lead to the downregulation of the ER.[7,10–12] Downregulation of the ER makes it unavailable for estrogen or other estrogen agonists to bind. Tamoxifen, by comparison, binds the ER but does not inactivate AF1 and therefore has partial agonist properties (Fig. 2).[13]

Early clinical trials demonstrated that even at low doses, fulvestrant downregulated ER expression to a significantly greater extent than tamoxifen.[9,13] Fulvestrant decreases estrogen-dependent progesterone levels compared with placebo and appears to have no estrogenic effects on the endometrium of healthy postmenopausal volunteers.[14] Conversely, tamoxifen causes an increase in progesterone receptor levels, and is well known to have estrogenic effects on the endometrium.[15] Because fulvestrant's mechanism of action differs from tamoxifen, activity is still demonstrable in tamoxifen resistant breast cancer cells both in vitro and in vivo.[10,16]

Fulvestrant does not affect serum levels of prolactin, sex hormone binding globulins or lipids. It is metabolized by multiple hepatic pathways and excreted in the feces with less than 1% excreted in urine. Metabolism is similar to other endogenous corticosteroids and includes oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or phosphate at the 2, 3, and 17 positions of the steroid nucleus, and oxidation of the sulphoxide side chain. Although human liver preparations treated with fulvestrant have shown that cytochrome P450 CYP 3A4 plays a role in the metabolism of fulvestrant, this is not the predominant pathway.[17] Thus, fulvestrant would not be expected to cause significant cytochrome P450 interactions with coadministered agents. Identified metabolites appear either less active or have similar activity as fulvestrant.[18]

The effect of fulvestrant appears dose dependent. Clinical studies have examined the effect of single doses of fulvestrant versus tamoxifen versus placebo on ER, PR, Ki67 proliferation associated labeling index (Ki67LI), and apoptotic index. Patients were given 50 mg, 125 mg, or 250 mg of fulvestrant. A dose dependent relationship was found between fulvestrant, ER, PR, and Ki67LI. There was no significant treatment effect on the apoptotic index. This may be related to the methodological challenges related to measuring the apoptotic index.[5,14]

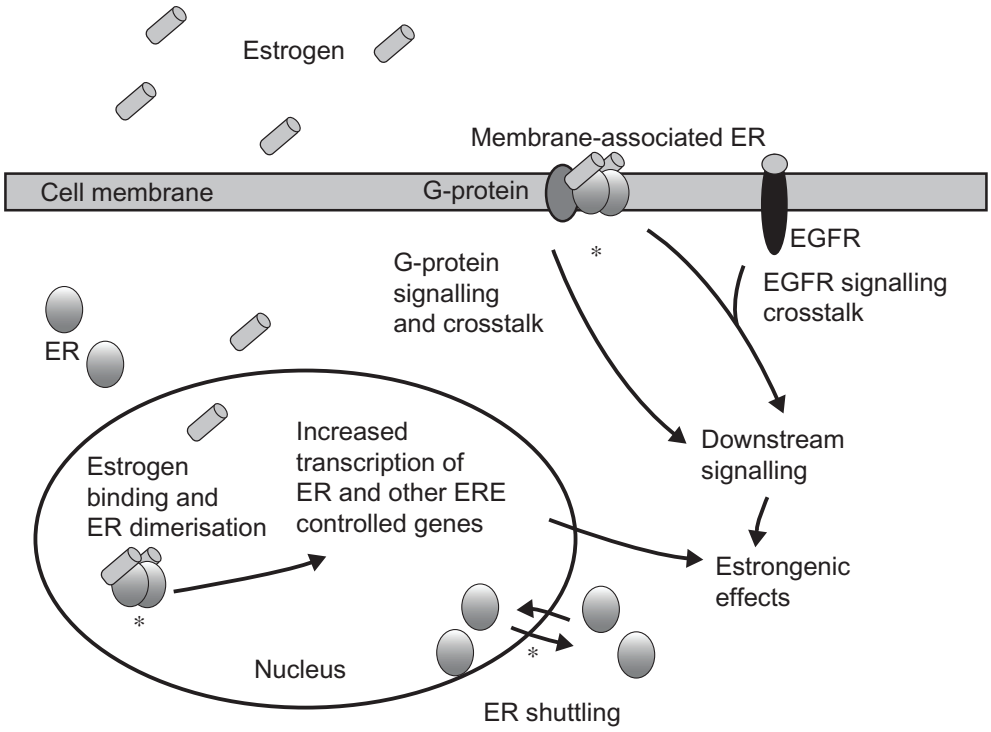

Figure 2. Mechanism of action of fulvestrant (From Osborne et al. Fulvestrant: an estrogen receptor antagonist with a novel mechanism of action).
Abbreviations: EGFR, epidermal growth factor receptor; ER, estrogen receptor; ERE, estrogen response element.

Howell et al demonstrated excellent tolerability of the standard 250 mg monthly dosing schedule in early phase I/II clinical trials of single agent fulvestrant.[19,20] No significant drug-related toxicity was observed in either study. Transient blood-stained vaginal discharge despite absence of other vasomotor symptoms and bromhidrosis (change in body odor) have been observed at low rates in subsequent studies.[21] Luteinizing hormone and follicle-stimulating hormone levels rose after withdrawal of tamoxifen and then plateaued, suggesting that fulvestrant does not affect the pituitary-hypothalamic axis. In addition there were no significant changes noted in serum levels of prolactin, sex hormone-binding globulin or lipids.[17]

Clinical Studies

Primary prevention

Xenograft models of breast cancer prevention suggest that fulvestrant may have similar or better efficacy than tamoxifen in preventing breast cancer.[22] There are, however, no clinical trials published to date addressing primary breast cancer prevention using fulvestrant in humans.

First-line therapy for advanced disease

Single-agent

Fulvestrant has been compared to tamoxifen in the first-line setting. In a phase III multinational, randomized, double blind study, 587 women with locally-advanced or metastatic breast cancer who had not received treatment for advanced disease were randomly assigned to fulvestrant 250 mg IM monthly (n = 313) or 20 mg tamoxifen orally daily (n = 274). Noninferiority of fulvestrant was not demonstrated in the overall population according to a predefined criterion (hazard ratio $\leq$1.25), but there was no significant difference in time to progression (TTP) at a median follow-up of 14.5 months (6.8 vs. 8.3 months for fulvestrant and tamoxifen respectively). There was a statistically significant advantage of tamoxifen over fulvestrant in adjusted overall survival (OS, 38.7 vs. 36.9 months respectively). Planned analysis performed on the hormone receptor positive subgroup disease did not show a difference in TTP or OS between the treatment groups (Table 1).[23]

Bartsch et al reported a similar overall TTP of 7 months in a mixed population of advanced breast cancer patients during a registry trial. Interestingly, in the subset analysis of patients receiving fulvestrant as primary therapy the median TTP was 9 months (range 2–34, 95% CI 8.5–9.5) approximating that seen among tamoxifen-treated patients.[24]

The FIRST (Fulvestrant first-line) study was conducted to compare a higher dose (HD) strategy (500 mg/month plus 500 mg on day 14 of month 1) based on evidence of dose-dependent clinical activity, improved time to peak tissue concentration, and excellent tolerance observed on previous trials at 250 mg/month dosing.[19] FIRST was a phase II open-label randomized multicenter study comparing HD fulvestrant versus anastrozole (1 mg/day) in the primary treatment of postmenopausal women with locally advanced or metastatic ER and/or PR positive breast cancer. The primary endpoint was clinical benefit (CB) defined as the proportion of all randomized patients who have a best overall response of a complete response, partial response or stable disease for at least 24 weeks. A total of 205 women were enrolled including 182 patients with measurable disease according to RECIST criteria. High-dose fulvestrant and anastrozole were similar with regard to clinical benefit rate (72% versus 67% respectively), and objective response rates (36% in both arms). TTP was longer with fulvestrant (median not reached) versus anastrozole (median 12.5 months) and 29% versus 41% had progressed at the time of data cut-off (hazard ratio = 0.63 95% CI 0.39–1.00) (Table 1).[25]

First-line therapy for advanced disease

Multi-agent

Combining fulvestrant and other targeted therapies presents an attractive opportunity to abrogate multiple specific pathways at relatively low toxicity. Though multiple fulvestrant-based combination therapies are currently under evaluation, including combinations with tyrosine kinase inhibitors, aromatase inhibitors, and angiogenesis inhibitors, among others, the only published data come from a phase II study of the farnesyltransferase inhibitor tipifarnib. Li et al reported the combination of fulvestrant (250 mg IM q28 days) and tipifarnib (300 mg PO BID days 1–21) produced CB rates similar to historical rates of fulvestrant alone (52%, 95% CI 34%–69%) in a mixed

Table 1. Summary of methodology and results for trials using fulvestrant as first-line adjuvant therapy.

Trial	Treatment arms	n	Type of trial	Inclusion criteria	Outcome	Measure	Comparison
Single agent							
Howell et al	Tamoxifen 20 mg PO daily	313	Phase III	Postmenopausal, metastatic or locally advanced breast cancer, no prior cytotoxic or endocrine therapy for advanced disease, no endocrine therapy in the last 12 months, hormone receptor status positive or unknown	TTP*	Tamoxifen 8.3 months	HR = 1.18 (95% CI 0.98 to 1.44)
	Fulvestrant 250 mg IM monthly		Double blind			Fulvestrant 6.8 months	p = 0.088
		274	Double-dummy				
			Randomized		TTP in HR positive	Tamoxifen 8.3 months	HR = 1.10 (95% CI 0.89 to 1.36)
						Fulvestrant 8.2 months	p = 0.39
					ORR	All	OR = 0.87 (95% CI 0.61 to 1.24)
						Tamoxifen 33.9%	p = 0.45
						Fulvestrant 31.6%	
						HR positive subroup	
						Tamoxifen 31.1%	
						Fulvestrant 33.2%	
					CBR	Tamoxifen 54.3%	p = 0.026
						Fulvestrant 62.0%	
					DOR	Tamoxifen 19.8 months	
						Fulvestrant 17.3 months	
					TTF	Tamoxifen 7.8 months	HR = 1.24 (95% CI 1.03 to 1.50)
						Fulvestrant 5.9 months	p = 0.026
					TTD	Tamoxifen 38.7 months	HR = 1.29 (95% CI 1.01 to 1.4)
						Fulvestrant 36.9 months	p = 0.04

(*Continued*)

Table 1. (*Continued*)

Trial	Treatment arms	n	Type of trial	Inclusion criteria	Outcome	Measure	Comparison
Bartsch et al (Data included for first-line patients only)	Fulvestrant 250 mg IM monthly	92	Phase II	Postmenopausal, metastatic breast cancer, all had failed prior endocrine therapy either as adjuvant treatment or for advanced disease, karnovsky performace status ≥70, hormone receptor status positive	TTP* ORR CBR	9 months 29.30% 75%	95% CI, 8.51–9.49 p = 0.037
Robertson et al (FIRST)	Fulvestrant 500 mg IM monthly plus 500 mg on day 14 of month 1 Anastrozole 1 mg PO daily	102 103	Phase II	Postmenopausal, metastatic or locally advanced breast cancer, no prior cytotoxic or endocrine therapy for advanced disease, endocrine therapy for early disease permitted if completed more than 12 months prior, at least one measurable lesion by RECIST criteria, WHO performance status of 0-2, hormone receptor status positive	CBR* ORR TTP DoCB DOR	Anastrozole 67.0% Fulvestrant 72.5% Anastrozole 35.5% Fulvestrant 36.0% Anastrozole 41.7% Fulvestrant 29.4% Anastrozole not reached Fulvestrant not reached Anastrozole 14.2 months Fulvestrant not reached	OR 1.30 (95% CI, 0.72 to 2.38) p = 0.386 OR 1.02 (95% CI, 0.56 to 1.87) p = 0.947 HR = 0.63 (95% CI, 0.39 to 1.00) p = 0.0496
Multiagent							
Li et al.	Fulvestrant 250 mg IM monthly and tiparfinib 300 mg twice daily for 21 every 28 days	33	Phase II	Postmenopausal, metastatic or locally advanced breast cancer, no prior cytotoxic therapy, at least one measurable lesion by RECIST criteria, ECOG performance status of 0–2, one prior fulvestrant dose acceptable but two not acceptable, initial protocol enrolled endocrine	CBR*	51.60%	95% CI, 34.0% to 69.2%

(*Continued*)

Table 1. (*Continued*)

Trial	Treatment arms	n	Type of trial	Inclusion criteria	Outcome	Measure	Comparison
				resistant disease, changed to no prior endocrine therapy after enrolling 8 patients, hormone receptor positive	TTP	7.2 months	95% CI, 5.2 to 19.4 months
					DOR	16.0 months	
					OS	19.4 months	95% CI, 16.1 to 27.6 months

*Primary endpoint.
Abbreviations: TTP, time to progression; ORR, objective response rate; CBR, clinical benefit rate; DOR, duration of response; TTF, time to treatment failure; TTD, time to death; HR, hormone receptor; IM, intramuscular; OS, overall survival; DoCB, duration of clinical benefit; HR, hormone receptor.

population of endocrine therapy resistant and naïve patients. Among a subset of patients with aromatase-inhibitor resistant disease, they reported CB in 48% (95% CI 26%–69%) of patients, suggesting a possible target population (Table 1).[26]

Second-line therapy for advanced disease

In the initial phase II trial, efficacy was demonstrated using a single-agent monthly dosing schedule of 250 mg as an intramuscular injection. Sixty-nine percent of 19 patients with tamoxifen-resistant disease experienced some clinical benefit (CB) at 6 months with the median duration of CB in excess of 18 months (CB = complete responses + partial responses + stable disease at 6 months). In this analysis there did not appear to be an association between duration of tamoxifen use and response to fulvestrant.[20]

Trial N0032, a phase II trial of 80 postmenopausal women with previously hormone sensitive tumors and RECIST-measurable disease who experienced disease progression after treatment with a third-generation aromatase inhibitor and at most one additional hormonal agent, demonstrated potential benefit of fulvestrant in "endocrine therapy resistant" disease. Ingle et al observed an objective tumor response rate of 14% in a mixed population of which 73% had received two prior hormonal treatments and 32% had undergone previous cytotoxic chemotherapy for metastatic disease; CB rate at 6 months was 35%. Among a small subset of tamoxifen-naïve patients the clinical benefit rate was 52%, suggesting that the efficacy of fulvestrant may be related to the number of prior hormonal agents used (Tables 2 and 3).[27]

Two phase III trials have demonstrated that fulvestrant is at least as effective as anastrozole in the treatment of postmenopausal women with advanced breast cancer who have developed resistance to tamoxifen. Study 0021 was a double-blind randomized trial conducted in North America. Four-hundred patients were enrolled and were given either fulvestrant 250 mg IM monthly or anastrozole 1 mg daily. All patients had locally advanced or metastatic breast cancer whose disease had progressed on adjuvant endocrine therapy for advanced disease and all had tumors that demonstrated hormonal sensitivity either with response to prior hormonal therapy or known ER or PR positivity. Patients were followed for a median duration of 16.8 months. No significant difference was demonstrated for TTP, objective response rate (ORR), CB rate, duration of response (DOR), or time to treatment failure (TTF).[28]

Study 0020 was conducted in Europe, South Africa, and Australia concurrently with 0021. It was designed similarly to 0021 but was blinded and gave the drug as 2 separate intra-gluteal injections. 451 patients received either 250 mg IM fulvestrant monthly or oral anastrozole 1 mg daily. The primary endpoint was TTP. After a median follow-up period of 14.4 months the median TTPs were not statistically different at 5.5 months in the fulvestrant group versus 5.1 months in the anastrozole group. No significant differences were observed in ORR, CBR, DOR, or TTF.[29]

A subsequent combined analysis was performed when greater than 75% of the patients had died (two years after initial publication of these two trials). This demonstrated no difference in median OS between

Table 2. Summary of methodology for trials using fulvestrant as second-line adjuvant therapy.

Trial	Prior treatment	Treatment arms	n	Type of trial	Inclusion criteria
Ingle et al (N0032)	Disease progression after no more than one hormonal agent in addition to AI, up to one prior adjuvant chemotherapy for metastatic diseae and prior trastuzumab allowed	Fulvestrant dose 250 mg IM monthly	77	Phase II	Postmenopausal, metastatic or locally advanced breast cancer, hormone receptor positive disease, life expectancy at least 3 months, ECOG performance status of 0, 1, or 2, measurable disease by RECIST criteria
Osborne et al (0021)	Disease progression during adjuvant endocrine therapy or first-line endocrine therapy	Anastrazole 1 mg PO daily Fulvestrant 250 mg IM monthly	194 206	Phase III Double blind Double-dummy Randomized	Postmenopausal, metastatic or locally advanced breast cancer, hormone receptor status positive, life expectancy greater than 3 months with hormone sensitivity, WHO performance status < or equal to 2, at least one measurable or nonmeasurable but assessable lesion
Howell et al (0020)	Disease progression during adjuvant endocrine therapy or first-line endocrine therapy	Anastrazole 1 mg PO daily Fulvestrant 250 mg IM monthly	222 229	Phase III Not blinded Randomized	Postmenopausal, metastatic or locally advanced breast cancer, hormone receptor status positive, life expectancy greater than 3 months, WHO performance status of < or equal to 2, at least one measurable lesion
Chia et al (EFECT)	Disease progression or relapse afer treatment with nonsteroidal AI	Exemestane 25 mg PO daily Fulvestrant 500 mg IM on day 0, 14, and 28 and 250 mg IM monthly thereafter	342 351	Phase III Double blind Double-dummy Randomized	Postmenopausal, metastatic or locally advanced breast cancer, hormone receptor status positive, WHO performance status of 0 to 2, life expectancy of at least 3 months and the presence of at least one measurable or assessable lesion. Initial protocol required lesion evaluable by RECIST criteria, but subsequently amended to include patients with bone lesions only

Abbreviations: AI, aromatase inhibitor.

fulvestrant and anastrozole (27.7 versus 27.4 months respectively).[30] A retrospective analysis was also performed examining the effect of fulvestrant versus anastrozole in patients with and without visceral metastases. Patients were divided into three groups: those with no visceral metastases, all patients with visceral metastases, and patients with visceral metastases only. The ORR and CBR was similar between fulvestrant and anastrozole in all three groups.[31]

The EFECT trial (Evaluation of Faslodex versus Exemestane Clinical Trial) compared the efficacy of fulvestrant versus exemestane, a steroidal AI in patients who had been previously treated with a non-steroidal AI. Exemestane 25 mg was administered once a day orally and fulvestrant was given with a loading dose (LD) of 500 mg on day 0, 250 mg on day 14 and day 28 followed by 250 mg monthly. The primary endpoint was TTP. Six hundred ninety-three women were enrolled, 342 to exemestane and 351 to fulvestrant LD. Median TTP was 3.7 months for both groups. ORR and DOR were also similar between both drugs.[32] A retrospective analysis on CB of exemestane and fulvestrant LD was also performed in patients with visceral involvement. Fifty-seven percent of patients in EFECT had visceral involvement. Fulvestrant LD and exemestane demonstrated clinical benefit in 29.1% and 27.2% of patients with visceral involvement, respectively. Neither the median duration of response (13.5 months for fulvestrant LD versus 10.8 months for exemestane) nor the median duration of CB (9.9 versus 8.1 months, respectively) were statistically different.[33]

Tolerability and Quality of Life

Across all of the phase III trials reviewed, fulvestrant was well tolerated. Withdrawal secondary to adverse effects (AEs) was 3.2% or less. The most common AEs were nausea, asthenia, injection site pain, headache, and vasodilation. In the phase III trials comparing tamoxifen and fulvestrant, patients using tamoxifen experienced more hot flashes than those using fulvestrant. This difference approached statistical significance. One patient died of pulmonary embolism, and this was thought to possibly be related to fulvestrant. Patients using anastrozole experienced more joint disorders than those using fulvestrant. There was no significant difference in the other side effects including thromboembolic disease, vaginitis, gastrointestinal disturbances, vasodilation, nausea, and headache (Table 4).[23,28,29,32]

One of the secondary endpoints of Study 0021 was to assess injection side effects. Twenty-seven percent of patients receiving fulvestrant and 23% of patients receiving placebo injection with anastrozole reported injection site reactions. Most of these reactions were felt to be injection site pain, reaction, and/or inflammation. One person in the fulvestrant group and two in the anastrozole group withdrew secondary to AEs related to injections.[28] Similarly only one patient in Study 0020 withdrew secondary to injection side effects.[29]

Quality of life was assessed using the Functional Assessment of Cancer Therapy—Breast (FACT-B) questionnaire in all the phase III trials reviewed here except the EFECT trial. The Functional Assessment of Cancer Therapy—Endocrine Symptom (FACT-ES) was used in the EFECT trial. All four trials showed that quality of life was maintained over the duration of treatment regardless of the treatment arm.[23,28,29,32]

Patient Preference

With similar tolerability but different routes of administration amongst the various endocrine agents now available in the treatment of advanced breast cancer, multiple studies have addressed patient preference. Fallowfield et al investigated patient preferences regarding injections versus tablets. The study enrolled 208 women who had had a breast cancer diagnosis for at least two years. Patients were given a hypothetical scenario in which they had the choice of two equally effective medications, one taken orally daily and one taken by injection monthly. Sixty-three per cent of patients preferred tablets, 24.5% preferred the injection and 12.5% had no preference. The most common reasons for injection preference were ease of adherence and convenience whereas the most common reasons for tablet preference were also convenience and dislike of needles. Despite the aversion to injectable treatment, 50% of patients admitted that they sometimes forgot to take their oral medication or chose not to take their medication suggesting that injectable therapy may be a mechanism to improve compliance.[34]

Place of Therapy

The goal in patients with advanced breast cancer is disease treatment while maximizing quality of life

Table 3. Summary of results for trials using fulvestrant as second-line adjuvant therapy.

Trial	Treatment arms	Outcome	Measure	Comparison
Ingle et al (N0032)	Fulvestrant	TRR*	14.30%	90% CI, 8.2% to 22.5%
		CBR	35.10%	90% CI, 26% to 45%
Osborne et al (0021)	Anastrazole	TTP*	Anastrozole 3.4 months	HR = 0.92 (95% CI 0.74 to 1.14)
	Fulvestrant			p = 0.43
			Fulvestrant 5.4 months	
		ORR	Anastrazole 17.5%	OR = 1.01 (95% CI 0.59 to 1.73)
			Fulvestrant 17.5%	p = 0.96
		CBR	Anastrozole 36.1%	p = 0.26
			Fulvestrant 42.2.%	
		DOR	Anastrozole 10.8 months	
			Fulvestrant 19.0 months	
		TTF	Anastrozole 3.3 months	HR = 0.96 (95% CI 0.77 to 1.19)
			Fulvestrant 4.6 months	p = 0.69
Howell et al trial 0020	Anastrazole	TTP*	Anastrozole 5.1 months	HR = 0.98 (95% CI 0.80 to 1.21)
	Fulvestrant		Fulvestrant 5.5 months	p = 0.84
		ORR	Anastrazole 15.7%	OR = 1.38 (95% CI 0.84 to 2.29)
			Fulvestrant 20.7%	p = 0.20
		CBR	Anastrazole 45.0%	p = 0.85
			Fulvestrant 44.6%	
		DOR	Anastrazole 14.5 months	
			Fulvestrant 15.0 months	
		TTF	Anastrazole 4.1 months	HR = 0.97 (95% CI 0.80 to 1.19)
			Fulvestrant 4.6 months	p = 0.81
Chia et al (EFECT)	Exemestane	TTP*	Exemestane 3.7 months	HR = 0.93 (95% CI 0.819 to 1.133)
	Fulvestrant		Fulvestrant 3.7 months	p = 0.65
		ORR	Exemestane 6.7%	OR = 1.12 (95% CI 0.578 to 2.186)
			Fulvestrant 7.4%	p = 0.736
		CBR	Exemestane 31.5%	OR = 1.03 (95% CI 0.72 to 1.487)
			Fulvestrant 32.2%	p = 0.853
			Visceral involvement	
			Exemestane 27%	
			Fulvestrant 29%	
		DOR	Exemestane 9.8 months	
			Fulvestrant 13.5 months	

Abbreviations: TRR, tumor response rate; TTP, time to progression; ORR, objective response rate; CBR, clinical benefit rate; DOR, duration of response; TTF, time to treatment failure.
*Primary endpoint.

Table 4. Tolerability of fulvestrant in phase III trials.

Trial	Withdrawal secondary to AEs (%)	Death due to drug-related AE
Treatment arms		
Howell et al		
Tamoxifen	0	0
Fulvestrant	1	1—pulmonary embolus
Howell et al 0020		
Anastrozole	1.3	NR
Fulvestrant	3.2	
Osborne et al 0021		
Anastrazole	2.6	NR
Fulvestrant	2.5	
Chia et al		
Exemestane	2.6	0
Fulvestrant	2	0

Abbreviations: AE, adverse effect; NR, not recorded.

with endocrine therapy prior to the institution of cytotoxic chemotherapy. Fulvestrant adds to the armamentarium of endocrine agents that can be used in this setting. It is currently being used in the second or third-line setting in the treatment of breast cancer, and has similar efficacy to tamoxifen, nonsteroidal and steroidal AIs based on clinical data though noninferiority to tamoxifen in the first-line setting could not be demonstrated. Preliminary data in the first-line setting has also demonstrated that its efficacy is similar to anastrozole. Evidence shows that sensitivity to other endocrine agents is maintained following treatment with fulvestrant.[35] Thus fulvestrant provides another effective, well-tolerated option in the sequence of endocrine therapies that can be used in advanced breast cancer. Further clinical trials will help determine the optimal sequence of endocrine agents in these patients.

In the neoadjuvant setting, fulvestrant delivered 14–21 days before surgery has been shown to decrease both ER and PR expression in postmenopausal women.[14] In premenopausal women, however, doses up to 750 mg may be required prior to surgical excision to impact receptor status or Ki-67 expression.[36,37] As of this writing, the National Institute of Health reports one completed trial and five ongoing trials evaluating the use of fulvestrant, alone or in combination, as neoadjuvant therapy prior to surgical resection.[38] There are no published data to date.

Conclusions

Fulvestrant is an estrogen receptor antagonist with no agonist properties. Its effect on cancer cells appears to be dose dependent. Its efficacy is comparable to tamoxifen and aromatase inhibitors, and it can be used in postmenopausal women with advanced breast cancer in patients who have developed resistance to prior agents. Its use in the first-line setting is currently under investigation. Fulvestrant is well tolerated compared to other endocrine agents. The main side effects include nausea, asthenia, injection site pain, vasodilation, and headache. Fulvestrant is thus an option in the treatment of postmenopausal women with hormone receptor positive breast cancer who have disease progression. This additional endocrine agent will help to maintain quality of life in these patients prior to the institution of cytotoxic chemotherapy.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

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