Fulvestrant in Heavily Pretreated Metastatic Breast Cancer: Is It Still Effective as a Very Advanced Line of Treatment?

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Abstract

Background: Over 75% of postmenopausal patients with metastatic breast cancer have hormone receptor-positive tumors. Endocrine therapy, with its more favorable toxicity profile than chemotherapy, is the preferred treatment modality for these patients.

Objectives: To assess our experience with fulvestrant, an anti-estrogen, in an advanced phase of treatment, after progression on the classical anti-estrogen (tamoxifen) and aromatase inhibitors

Methods: The study group comprised 46 patients with metastatic breast cancer treated with fulvestrant during the years 2002–2006. Fulvestrant was given monthly until disease progression or unacceptable toxicity.

Results: The median number of fulvestrant cycles was 4.14 (range 1–32). Four patients are still on the treatment. The reasons for treatment discontinuation include disease progression (n=40), refusal (n=1), and allergic reaction (n=1). Ten patients (22%) achieved partial response and 22 (47%) had stable disease. Fourteen (30%) had disease progression with a response rate of 22% and a clinical benefit of 67%, and 14 (30%) had stable disease for > 6 months. Twenty-five patients (54%) are still alive, 4 (9%) without and 21 (45%) with disease progression. With a median follow-up of 15 months (range 1–30.1), the median time to progression was estimated to be 4 months (95% confidence interval 3.1–4.9), and the estimated overall survival 20.1 (95% CI 13.6 to upper limit; not reached yet). The 1 year estimated survival is 67%.

Conclusions: In terms of late-phase administration, fulvestrant still appears to have a good clinical effect, with a time to progression of 4 months and a clinical benefit > 60%, notably accompanied by only very mild toxicity. Irrespective of the line of treatment the patients received, the 4 month time to progression was constant and the medication was still working effectively in a very late line of treatment in metastatic breast cancer. Fulvestrant offers clinical benefit with very mild toxicity in a very heavily pretreated population and the medication is recommended, even in patients who received many lines of chemotherapy.

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Breast cancer remains a leading cause of cancer death in women despite continuing improvement in screening, prevention and treatment. The development of many effective tools has changed the nature of the treatment of metastatic breast cancer into long-term palliative management, where both quality of life and survival are important parameters in decision making. More than 75% of the affected postmenopausal patients have hormone receptor-positive tumors, and for these patients endocrine therapy with its more favorable toxicity profile as compared to chemotherapy is the preferred treatment modality. The patients' quality of life depends on the number of available endocrine treatments and, possibly, on the correct sequencing of the treatments with the intent to avoid cross-resistance and cumulative toxicities. Tamoxifen (an oral selective estrogen receptor modulator) was for many years the drug of choice, but new drugs have since been developed, among them second and third-generation non-steroidal (anastrozole, letrozole, etc.) and steroidal aromatase inhibitors (exemestane). Tamoxifen and aromatase inhibitors are usually used as first and second-line treatment for metastatic breast cancer, yielding good response rates with reduced toxicity compared to chemotherapy.

Patients with metastatic breast cancer will eventually progress while they are on the first and second-line drugs, although they still might be responsive to endocrine therapy. Fulvestrant is another drug that was recently introduced into this setting. It acts as an anti-estrogen that binds to and degrades the estrogen receptor and has estrogen antagonistic activity but no estrogen agonistic effect [1,2]. Treating patients with multiple lines of hormonal therapy seems to be effective, but there is little information about the activity of hormonal therapy after progression on aromatase inhibitors [3]. Exemestane elicited some response in patients previously exposed or not exposed to tamoxifen [4]: one phase II study reported a 4.8% response rate and 15.6% stable disease with exemestane following non-steroidal aromatase inhibitors [5]. Fulvestrant has been shown in two prospective randomized phase III clinical trials to be at least as effective as anastrozole in postmenopausal women whose disease had progressed on prior hormonal therapy [6-8]. Ingle et al. [3,4,9] reported a 14.3% response rate and 20.8% stable disease with fulvestrant in women with advanced breast cancer who had experienced disease progression on a third-generation aromatase inhibitor. In another phase III double-blind double-dummy study [10], fulvestrant evoked significant activity (66% clinical benefit) after progression on tamoxifen and vice versa (57% clinical benefit with tamoxifen after fulvestrant). In that study, patients who had not responded to first-line therapy still had a significant response to the other drug, thereby showing a lack of cross-resistance.

It is important to develop additional non-cross-resistant

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CI = confidence interval

endocrine therapies with no or negligible cumulative toxicities to increase the time during which patients can be treated and respond to active and less toxic regimens. In parallel, we need to determine the correct sequencing of the different endocrine therapies in order to achieve the best and the longest possible response prior to moving on to chemotherapy.

In this retrospective analysis of heavily pretreated patients with metastatic breast cancer, we report our experience with fulvestrant in an advanced phase of treatment.

Patients and Methods

We conducted a retrospective chart analysis of all patients with metastatic breast cancer who had been treated with fulvestrant between 2002 and 2006 in the Department of Oncology, Tel Aviv Sourasky Medical Center (Israel). Most of the women had been heavily pretreated and were exposed to a number of hormonal and chemotherapeutic agents prior to taking fulvestrant [Table 1]. The study subjects had histological or cytological proof of breast cancer with measurable or assessable disease (bone, pleural effusion, etc.). The tumors were estrogen and/or progesterone-receptor positive. A postmenopausal status was required and determined according to one of the following two criteria: a) at least 12 months since the last menstrual period, and b) prior castration (including luteinizing hormone-releasing hormone agonist injections in one patient).

Entry criteria required that the patients have an ECOG (Eastern Cooperative Oncology Group) performance score of 0–3 and a life expectancy of at least 3 months. They all had to show progression on any line of hormonal or chemotherapy, and could have been previously exposed to several lines of treatment in the adjuvant or metastatic setting. Patients were considered to have developed disease progression on tamoxifen if recurrence had been identified within 12 months of adjuvant tamoxifen or while on tamoxifen for the disease.

The patients were treated with fulvestrant (Faslodex®; AstraZeneca Pharmaceuticals, Wilmington, DE, USA) 250 mg in 5 ml of solution from a prefilled syringe as a single intramuscular injection into the gluteus maximus muscle of at least 2 minutes. The intervals to retreatment were 28 ± 3 days. There were no indications for dose modifications due to adverse events. Treatment was discontinued if there was evidence of disease progression or at the patient's request. Duration of treatment was dependent on response. All patients were assessable for toxicity, and the ones who received at least two courses of therapy were assessable for response.

Table 1. Patient characteristics

	Patients (n)	%
Age at enrollment (range, yrs)	61 (32–84)	
Receptor status		
ER+/PR+	29	63
ER+/PR-	16	34
ER-/PR+ positive	1	2.2
HER-2/neu status, primary or metastatic disease		
Not done	25	55
Her-2/neu weakly positive	15	32
FISH amplified, IHC +2-3	6	13
Prior hormonal treatments (adjuvant or metastatic setting)		
None	5	11
Tamoxifen in metastatic setting	38	82
Tamoxifen with one or more aromatase inhibitors		
Anastrozole	29	63
Letrozole	29	63
Exemestane	23	50
Megestrole acetate	10	21
Lanterone	5	11
Prior chemotherapy treatments		
Adjuvant	15	32
Metastatic setting	26	56
ECOG performance status		
0	18	39
1	21	45
2	5	11
3	2	5
Metastatic sites (n)		
≤ 1	10	36
≥ 2–5	36	21
Dominant disease site		
Visceral	37	80
Bone metastases	33	71
Lung/pleura metastases	13	28
Liver metastases	12	26
Other	28	60

FISH = fluorescent in situ hybridization

Evaluation of response

Since the patients had metastatic disease the treatment goals were palliation and delay of disease progression. After initiation of therapy the patients were assessed at 1 and 3 months, and every 3 months thereafter by physical examination, blood tests, and whatever investigations were deemed necessary by the treating physician. Treatment was continued until the identification of breast cancer progression. In accordance with World Health Organization criteria, a complete response was defined as the complete disappearance of all measurable disease for at least 4 weeks, and a partial response as a ≥ 50% reduction in the measurement of each palpable lesion. Disease progression was defined as a ≥ 25% increase in the measurement of any lesion documented within 8 weeks from the start of treatment or the appearance of any new lesion.

The time to tumor progression was defined as the time from the first day of fulvestrant treatment to the first sign of disease progression. Overall survival was calculated from the first day of fulvestrant treatment to the last visit or death, including death from any cause. Adverse events were evaluated according to National Institutes of Health common toxicity criteria.

Statistics

Statistical analysis was performed to assess the tumor response rate and toxicity profile of fulvestrant as a treatment for women whose breast cancer had progressed on previous lines of treatment. The primary endpoint of this analysis was tumor response rate and time to progression. The tumor response rate was defined as the total number of eligible patients who achieved a complete or partial response according to the WHO criteria divided by the total number of eligible patients enrolled into the study. The clinical benefit rate was determined by the total number of eligible patients who achieved a complete or partial response plus those who had stable disease. Time to progression and survival were analyzed by the Kaplan-Meier method and comparisons were made by the log-rank test. All tests were two sided and considered significant at $P < 0.05$.

Results

Altogether, 46 women were treated with fulvestrant in our institute between 2002 and 2006. The cohort's median age was 61 years (range 32–84) and the median ECOG performance status was 1 (range 0–3). Characteristics of the 46 patients at the time of the first fulvestrant administration are listed in Table 1. All patients had metastatic breast cancer with 1 to 5 sites of metastasis: 10 patients (22%) had one site and 36 (78%) had 2–5 sites. The disease was predominantly visceral in 37 patients (80%), bone in 33 patients (71%), lung and pleura in 13 (28%), liver in 12 (26%), and other sites in 28 (60%). The group's hormonal status was as follows: 29 (63%) were ER+/PR+, 16 (34%) were ER+/PR-, and one (2.2%) was ER-/PR+. Fifteen patients (32%) had Her-2 (0–1), 6 (13%) had Her-2 +2, +3 or amplified on fluorescent in situ hybridization, and 25 (55%) had unknown Her-2.

The patients had been previously exposed to a median of two hormonal lines (range 1–6), including adjuvant tamoxifen that had been given within 12 months of recurrence and a median of one chemotherapy line (range 0–6), or to a median of three lines of either modality (range 1–10) prior to treatment with fulvestrant. Thirty-eight patients (82%) had been exposed to tamoxifen, 37 (80%) to tamoxifen and any aromatase inhibitor, one (2.2%) had not received an aromatase inhibitor prior to fulvestrant and 6 (13%) were not exposed to tamoxifen in the metastatic breast cancer setting

Forty-one patients (89%) had been exposed to tamoxifen in an adjuvant or metastatic setting for a median of 36 months (range 7–144). Twenty-nine (63%) were treated with anastrozole for a median duration of 8 months (range 3–50), 29 (63%) were treated with letrozole for 6 months (range 2–30), 23 (50%) were treated with exemestane for 4 months (range 2–10), 10 (21%) were treated with megesterol acetate for 4.5 months (range 1–18), and 5 patients (11%) were treated with Lentaron® for a median duration of 12 months (range 4–54).

Fifteen patients (32%) had undergone adjuvant chemotherapy and 26 (56%) were exposed to chemotherapy in the metastatic setting with a median of one line (range 0–6). The median number of fulvestrant cycles was 4.14 (range 1–32).

Table 2. Response to fulvestrant

Response	Patients (n)	%
Partial response	10	22
Stable disease	22	47
Clinical benefit (partial response+ stable disease)	32	69
Disease progression	14	31

Four patients are still on treatment. The reasons for treatment discontinuation include disease progression (37 patients), refusal (one patient), allergic reaction (one patient) and rapid clinical deterioration (3 patients).

Ten patients (22%) achieved a partial response and 22 (47%) had stable disease. Fourteen (30%) had disease progression with a response rate of 22% and a clinical benefit of 67%, and 14 (30%) had stable disease that was sustained for more than 6 months. The response rate, time to progression, and survival data are presented in Table 2. At last contact, 25 patients (54%) were alive, 4 (9%) did not have disease progression and 21 (45%) did. Forty-five of the study patients received a median of two additional treatments after fulvestrant (range 0–4). With a median follow-up duration of 15 months (range 1–30.1), the median time to progression was estimated as 4 months (95% confidence interval 3.1–4.9), and the estimated overall survival as 20.1 (95% CI 13.6 to upper limit, not yet reached) [Figure 1]. The 1 year estimated survival was 67%.

We divided the patients into two groups: bone metastasis only (13 patients, 4 of whom died) and all other metastases (34 patients, 16 died). There was no statistical difference in response (59% and 69%, respectively) and the median survival of the groups was 597 and 604 days respectively ($P = 0.19$), although the number of patients with bone involvement only is too small to arrive at any firm conclusion.

The response according to Her-2/neu(Erb B2) (staining by immunochemistry) was 61.7% (95% CI 47.3–76): 59.1% (95% CI

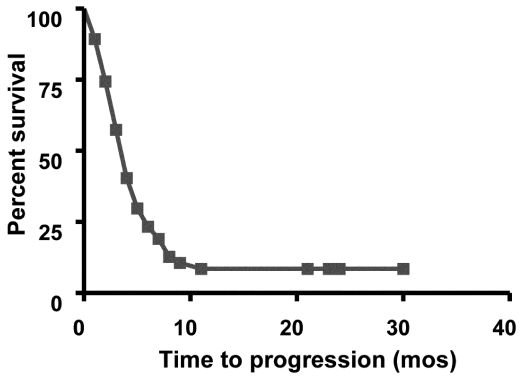

Figure 1. Time to tumor progression

ECOG = Eastern Cooperative Oncology Group
ER = estrogen receptor
PR = progesterone receptor

36.8–81.4) in patients with Her-2-negative (0,+1) and 64.0% (95% CI 43.7–84.2) in patients with Her-2-positive (+2,+3).

The response rate to Faslodex® (fulvestrant) in patients with only negative estrogen receptor was 40.0% (95% CI 28–108%; the large range of this CI is due to the small size of the group, i.e., 5 patients) and 64.2% (95% CI 49.1–79.4) in patients with positive estrogen receptor. The response rate to Faslodex in patients with negative progesterone receptor was 61.1% (95% CI 36.8–86.0) and 64.0% (95% CI 43.8–84.2) in patients with positive progesterone receptor. There was no significant difference between responders and non-responders to Faslodex with regard to tamoxifen response time, aromatase inhibitors response time and the combined response time.

Toxicity

All 46 patients were evaluable for toxicity. Overall, the level of toxicity was mild and patients rarely complained. The adverse events associated with the treatment are listed in Table 3. Grade II toxicity was rare and no grade III toxicities were noted (National Cancer Institute Common Toxicity Criteria version 3.0). Grade II anemia was reported in one patient (2.2%), mild hot flashes in 16 (34%), mild arthralgia and muscle pain in 20 (43%), allergic reaction (skin) in 2 (4.4%), transient pain in the injection site in 15 (32%), temporary loss of libido in 4 (9%), and mild depression in 13 (28%) that was not necessarily related to fulvestrant.

Table 3. Adverse events (grade I-II) during fulvestrant treatment

Adverse events	Patients (n)	%
Anemia	1	2.2
Hot flashes	16	34
Arthralgia, muscle pain	20	43
Skin allergic reaction	2	4.4
Pain in injection site	15	34
Loss of libido	4	9
Depression*	13	28

* Not necessarily associated with the medication

Discussion

Fulvestrant (Faslodex, ICI 182,780), first believed to be a pure anti-estrogen, has been in development for a number of years but progress was held back because of lack of availability of an oral formulation. Fulvestrant was most commonly studied as an intramuscular injection of 250 mg once monthly, and there has been some concern that this dosing level may not be quite adequate [9]. Loading with 250 mg every 2 weeks for three to four injections, followed by dosing at 250 mg/monthly, resulted in steady-state kinetics far more quickly than did monthly dosing. Subsequently, two large phase III clinical trials for comparing fulvestrant with anastrozole were opened in North America [10] and in a sub-study [11]. The North American trial (0021) was a double-blind study, whereas the sub-study (0020) was an open-label study. These studies included 851 postmenopausal patients with advanced breast cancer who had relapsed or progressed after endocrine therapy. Combined data from the two studies, which were designed to be analyzed together, showed no difference in time to progression (5.5 months for fulvestrant versus 4.1 months for anastrozole) and no significant difference (4.6 months for fulvestrant versus 3.6 months for anastrozole). The trend to benefit for fulvestrant in terms of time to progression and time to tumor failure, however, was greater in the North American [10] than in the sub-trial [11] but was not significant for the pooled data. Adverse effects, including vasodilation, injection site pain and nausea, were virtually identical in the two treatment arms. Withdrawals due to drug-related adverse events were 0.5% in the fulvestrant arm and 1% in the anastrozole arm. The incidence of thromboembolic events, weight gain and vaginitis were low for both treatments.

Thus, fulvestrant represents the first in a new class of drugs that bind, block and degrade the estrogen receptor. Fulvestrant offers a new treatment option for postmenopausal women with advanced breast cancer. It is the only anti-estrogen to have demonstrated a clinical benefit in over 40% of patients whose disease had progressed or relapsed after previous tamoxifen therapy. It is at least as effective as the third-generation aromatase inhibitors in women who had previously received tamoxifen. Both phase III trials of fulvestrant versus anastrozole demonstrate at least equivalent and perhaps greater benefit over anastrozole for all major efficacy endpoints. Fulvestrant, despite its intramuscular route of administration, is well tolerated and has few adverse events [12].

As mentioned earlier, fulvestrant exhibited antitumor activity in postmenopausal women with metastatic breast cancer that progressed on prior therapy with tamoxifen or third-generation aromatase inhibitors [9]. Two-thirds of the women had clinical benefit, and more than one-third obtained benefit by virtue of achieving a partial response (14.3%) or having stable disease for at least 6 months (20.8%). We report a 22% response rate with 67% clinical benefit in a group of heavily pretreated patients who had a median of two previous hormonal lines (range 1–5) and one previous chemotherapy line (range 0–6).

We are aware that our study is limited by being small and retrospective, and that treatment prior to fulvestrant was non-homogeneous among our subjects, although most of them (82%) were exposed to tamoxifen and aromatase inhibitors. We can, however, learn from our results about appropriate sequencing of hormonal therapies, especially the optimal positioning of fulvestrant. We demonstrated that, in terms of late-phase administration, fulvestrant still appeared to have an effect, with a median time to progression of 4 months and a clinical benefit > 70%, notably accompanied by only mild toxicity.

Since radiological studies were not performed according to a scheduled plan, we did the evaluation once a month according to clinical evaluation, markers (CEA and CA15.3) and imaging according to clinical indication.

The issue of toxicity takes on special importance when considering the generally poor physical condition of this very heavily pretreated group of women with long-lasting disease. Our results

demonstrate that fulvestrant offers clinical benefit with very mild toxicity in a very heavily pretreated population.

Most of the patients (78%) had more than one site of metastasis and 80% had predominantly visceral diseases. We did not find any correlation with the site of metastasis (bone or others) or Her-2/neu staining, although we performed only immunohistochemistry because this is an 'old group' of breast cancer patients.

Today we may begin the treatment of metastatic breast cancer in postmenopausal women with a different endocrine cascade, whereas in the past we would have started with and progressed on tamoxifen. Fulvestrant is an adequate treatment as the aromatase inhibitors move to the position of first-line therapy. We will, however, require more data on the efficacy of administering fulvestrant after aromatase inhibitors to determine the most appropriate sequence of hormonal therapy. Currently, agents such as megestrol acetate have been relegated to fourth and fifth-line therapies, and agents such as estrogen have been nearly forgotten. Considering that aromatase inhibitors produce a very low estrogen environment, it will be important to explore the role of fulvestrant, an estrogen down-regulator, and determine whether this may be more or less useful in this setting than other approaches. Perhaps drugs such as estrogen should now be reexamined in this setting. The results of investigations in which an aromatase inhibitor is combined with fulvestrant will be of great interest.

In summary, the endocrine cascade in postmenopausal women remains somewhat undetermined. It is probably most prudent to start with tamoxifen followed by an aromatase inhibitor or begin with an inhibitor followed by tamoxifen and – in either case – follow this course by fulvestrant as a third-line therapy. Another option is to consider using fulvestrant as second-line therapy instead of the aromatase inhibitor.

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