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The Role Of Fulvestrant In Therapy Of Metastatic Breast Cancer

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ABSTRACT

Metastatic breast cancer (mBC) is a chronic incurable disease that requires long-term systemic treatment with regular changes in drugs. Hormone-dependent (luminal) subtype of mBC is treated mainly with endocrine therapy, which allows achieving the effect with less toxicity compared to chemotherapy.

Objective. To evaluate the efficacy and tolerability of fulvestrant in patients with mBC after previous treatment.

Methods. A single-center study was conducted, which included 20 patients with HR+ metastatic BC who showed disease progression after previously received therapy (adjuvant or systemic for mBC). Inclusion criteria: postmenopausal status, positive tumor receptor status (ER and/or PR), ECOG performance status index ≤ 2, preserved liver, kidney and bone marrow functions. Fulvestrant was administered intramuscularly at a dose of 500 mg monthly with a loading dose of 500 mg on the 14th day of the first cycle.

Results. The overall clinical efficacy (disease control) was 65%: partial tumor regression was achieved in 2 patients (10%), disease stabilization

was achieved in 11 patients (55%), and progression was noted in 7 patients (35%). The median time to progression (PFS) was 6 months. One-year progression-free survival was 45%. The median overall survival was not reached during the follow-up period; one-year OS was ~70%. Adverse events were predominantly mild or moderate: asthenia in 80% of patients, hot flashes in 25%, headache and nausea in 20%. No severe toxic reactions (≥grade 3) were noted.

Conclusions. The obtained results support the use of fulvestrant (500 mg) as an important option for hormonal therapy of mBC after disease progression.

Keywords: Metastatic breast cancer; hormone-dependent cancer; fulvestrant ; endocrine therapy; efficacy; survival; toxicity.

INTRODUCTION

Breast cancer (BC) is a leading cancer morbidity among women worldwide, accounting for about a quarter of all malignant neoplasms in women. About 2 million new cases of BC are diagnosed worldwide annually, and approximately 700,000 women die from this disease. In developed countries, every 8–12th woman is diagnosed with BC during her lifetime. Despite the success of early diagnosis and treatment, a significant proportion of patients subsequently develop a metastatic process. Distant metastases occur in about 50% of women who have had early BC, at various times after the end of primary treatment. In addition, about 8% of patients have a disseminated process already at the time of primary diagnosis (stage IV). Metastatic BC (mBC) remains virtually incurable: even with modern capabilities, the median overall survival of patients with mBC is about 2–3 years [1,3]. According to large studies, only about 20–25% of patients with mBC are alive 5 years after the diagnosis of metastatic lesions. Thus, mBC is currently considered a chronic disease that requires long-term therapy with a consistent change in treatment methods as it progresses. The main goals of metastatic therapy are to prolong the patient's life as much as possible and maintain its quality [4].

The most important factor determining the treatment tactics for breast cancer is the biological (molecular) subtype of the tumor. About 60-70% of breast cancer cases belong to the hormone-dependent subtype, characterized by the expression of estrogen and/or progesterone receptors (ER/PR-positive, the so-called luminal subtype). Patients with this subtype in the metastatic form of the disease have a high chance of responding to endocrine (hormonal) therapy. Endocrine therapy is the preferred option for systemic treatment of luminal mBC , as it provides comparable efficacy to chemotherapy with significantly better tolerability and quality of life for patients. The use of chemotherapy is usually reserved for hormone-resistant cases or rapidly progressing disease [7,9].

Classic hormone therapy agents for breast cancer are selective estrogen receptor modulators (SERMs), such as tamoxifen , and aromatase inhibitors (anastrozole, letrozole, exemestane) in postmenopausal patients. Tamoxifen has been the gold standard for treating ER+ breast cancer for many years, but it has partial agonist properties, i.e., an estrogen-like effect in some tissues (e.g., the endometrium), which can lead to undesirable effects and reduce the effectiveness of therapy. In this regard, a fundamentally different class of drugs was developed – selective inhibitors of estrogen receptor degradation (SERD), devoid of agonist activity [11].

Fulvestrant is a representative of the SERD class, a "pure" antagonist of the estrogen receptor, completely blocking its function. The mechanism of action of fulvestrant is high-affinity binding to ER, leading to rapid degradation of the receptor and cessation of transmission of estrogen-dependent proliferative signals in the tumor cell. Unlike tamoxifen , fulvestrant does not have an estrogen-like (agonist) effect, due to which it does not stimulate tumor cell growth and does not cause side effects characteristic of SERDs from hormone-sensitive tissues. The drug was initially approved for the treatment of metastatic breast cancer in patients with disease progression after tamoxifen therapy . Later, its use was extended to cases of resistance to aromatase inhibitors , as well as to the first line of mBC therapy [8,10].

Initially, fulvestrant was used at a dose of 250 mg per month, but the CONFIRM study demonstrated the advantage of a double dose. In this large randomized study , fulvestrant at a dose of 500 mg showed statistically significantly higher efficacy, prolonging the median time to progression and

median overall survival of patients compared with a dose of 250 mg. Thus, the median overall survival was 26.4 months with 500 mg versus 22.3 months in the 250 mg group (p = 0.02). At the same time, the safety profile did not differ in both doses. Today, a dose of 500 mg monthly is the standard for fulvestrant [6,13].

The efficacy of fulvestrant is comparable to that of modern hormonal agents. In particular, the FIRST study demonstrated that in patients with mBC who had not previously been treated with endocrine therapy [9,12], the median time to progression on fulvestrant 500 mg reached 23.4 months, which was significantly higher than the same indicator in the anastrozole group (13.1 months). This indicates the high activity of fulvestrant in first-line therapy. At the same time, the optimal sequence of fulvestrant use and its role in combinations remain the subject of study [1,2]. A modern trend in the therapy of hormone-positive mBC is a combination of endocrine agents with targeted drugs, primarily with cyclin-dependent inhibitors kinases 4/6 (palbociclib, ribociclib, abemaciclib). Adding a CDK4/6 inhibitor to fulvestrant nearly doubled the median PFS compared to monotherapy fulvestrant (9.5 vs 4.6 months in the PALOMA-3 study), also improving overall survival [4,5]. However, even in the era of combinations, monotherapy Fulvestrant retains its niche as an effective and well-tolerated treatment option, particularly in patients with limited metastatic disease or who are intolerant/unavailable to combination therapy.

Based on the above, it is of interest to analyze the results of using fulvestrant in patients with mBC who previously received various types of treatment. This work is devoted to assessing the efficacy and safety of fulvestrant in real clinical practice in a group of patients with mBC [3,11].

Objective of the study

The objective of the study was to evaluate the clinical efficacy (antitumor effect, survival rates) and tolerability of fulvestrant in the treatment of metastatic breast cancer in patients with previous antitumor therapy.

METHODS

Study design: a retrospective single-center case series study. Medical data of patients with mBC who received fulvestrant in an oncology institution were reviewed. Inclusion criteria: histologically verified breast cancer with distant metastases, ER and/or PR expression in the tumor (luminal subtype), postmenopausal status, previous treatment (adjuvant and/or systemic for mBC) with subsequent disease progression, general condition according to ECOG 0–2, satisfactory function of major organs and systems (liver, kidneys, bone marrow). Patients with HER2-positive tumor status requiring specific anti-HER2 therapy, as well as patients with life-threatening visceral metastases requiring immediate chemotherapy were not included. All patients received fulvestrant (Faslodex) according to the standard regimen: 500 mg intramuscularly once every 28 days with an additional 500 mg on day 14 of the first cycle. Therapy was carried out until confirmed disease progression or unacceptable toxicity. The duration of fulvestrant treatment was recorded in each case (in months). In case of progression, patients were prescribed subsequent lines of therapy at the discretion of the attending physician (chemotherapy or other endocrine therapy options, including combinations with targeted drugs). The primary efficacy endpoint was the immediate antitumor effect, assessed by the best tumor response to treatment in accordance with the RECIST 1.0 criteria. The achieved effect was classified as complete regression (CR), partial regression (PR), disease stabilization, or disease progression. Secondary efficacy endpoints were progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from the start of fulvestrant therapy to the development of disease progression or death; OS was defined as the time from the start of therapy to the patient's death (regardless of the cause). The Kaplan-Meier method was used to estimate the time to the event, calculating the median and the proportion of survivors at fixed milestones (6 months, 12 months). Comparative analysis of subgroups (depending on patient characteristics or previous therapy) was not performed due to the small sample size. Adverse events (AE) registered during therapy and their maximum grade according to CTCAE v4.0 were analyzed. Particular attention was paid to side effects typical of hormonal therapy: hot flashes, asthenia, gastrointestinal symptoms, etc. Severe toxic reactions (grade 3-4) were considered separately. The data were processed using descriptive statistics. Categorical indicators are presented as absolute numbers and percentages. Median times to events were estimated using the Kaplan – Meier method with 95% confidence intervals (95% CI) provided. Statistical software: Statistics for Biomedical Research v2.3.

RESULTS

The analysis included data from 20 women with metastatic HR+ BC. The mean age of the patients was 58 years (range 45–72 years). Internal organ involvement (liver and/or lungs) was observed in 12 patients (60%), while 8 patients (40%) had only bone metastases ± soft tissue involvement. Previous antitumor therapy varied: 6 patients (30%) received only adjuvant treatment before mBC development (including 3 patients who received adjuvant hormonal therapy with tamoxifen and 3 patients who received adjuvant chemotherapy); 14 patients (70%) had previously been treated for mBC (including 5 patients after progression on tamoxifen , 4 patients after aromatase inhibitors , and 5 patients after chemotherapy for metastatic disease) (Table 1).

Table 1. Characteristics of patients included in the analysis

Indicator	Quantity
Damage to internal organs (liver/lungs)	12 (60%)
Bone ± soft tissue metastases	8 (40%)
Adjuvant treatment only (before mBC)	6 (30%)
- Adjuvant hormone therapy (tamoxifen)	3
- Adjuvant chemotherapy	3
Previous treatment mBC	14 (70%)
- After progression on tamoxifen	5
- After inhibitors aromatase	4
- After chemotherapy	5

Thus, fulvestrant was used as second-line therapy and further in all included patients, including cases of progression after at least one course of hormonal therapy (tamoxifen or AI) or chemotherapy. According to the results of the best response to fulvestrant, overall disease control (partial regression + stabilization) was achieved in 13 of 20 patients (65%). Partial tumor response (PR) was observed in 2 patients (10%), both cases in patients with exclusively bone metastases. Disease stabilization for at least 6 months was recorded in 11 patients (55%). Progression of the process against the background of fulvestrant therapy was noted in 7 patients (35%). Objective complete regressions (CR) were not registered in this sample (Table 2). The distribution of immediate therapy results is presented in Table 1 (PR - 10%, stabilization - 55%, progression - 35%).

Table 2. Fulvestrant response results

Exodus treatments	Quantity patients (n)	(%)
Partial regression	2	10
Stabilization	11	55
Progression	7	35
Complete regression	0	0

When analyzing the effectiveness depending on the type of previous therapy, no significant differences were found due to the small size of the subgroups. However, it is noteworthy that cases of partial regression were achieved after previous hormone therapy (tamoxifen), while most progressions were observed in patients who had previously received chemotherapy for mBC . These trends require confirmation in a larger sample.

The median time to progression on fulvestrant was 6.0 months (95% CI 4.2–7.8). At 12 months from the start of therapy, 45% of patients remained progression-free (1-year PFS = 45%). Two patients continue to take fulvestrant without signs of progression at the time of data analysis; their treatment duration to date is 30 and 32 months, respectively (both cases - metastases only to bones). In 14 patients (70%), disease progression occurred within the first 6 months of therapy, in another 3 patients (15%) - in the period from 7 to 15 months.

fulvestrant treatment were distributed as follows: partial regression (PR) was achieved in 2 patients (10%), disease stabilization – in 11 (55%),

progression – in 7 (35%). No complete regressions were observed. Thus, the overall efficacy (clinical benefit) was 65% (13/20 patients had disease control ≥6 months). It is noteworthy that both cases of PR were registered in patients with isolated bone metastasis. Conversely, out of 7 cases of progression, 5 patients had visceral metastases, and 2 had bone metastases. The ratio of PR, stabilization and progression cases is graphically shown in Figure 1 (diagram of distribution of results).

fulvestrant administration in different patients ranged from 3 to 32 months. In 14 patients (70%), disease progression occurred in the first 6 months of therapy, and in another 3 patients (15%), within 7 to 15 months. At the date of the last observation, 2 patients (10%) continued treatment without signs of progression for 30 and 32 months. The median time to progression in the entire group was 6.0 months (95% CI 4.4–7.6). One-year progression-free survival (the proportion of patients without progression after 12 months of therapy) was 45% (Table 3).

Table 3. Duration of therapy and survival rates

Indicator	(%)
Progression in the first 6 months	14 (70%)
Progression in the 7-15 month interval	3 (15%)
Continuation of therapy without progression (>30 months)	2 (10%)
1 year non-progressive survival	1 (5%)

At the time of data analysis, the median overall survival had not been reached (8 deaths out of 20 were observed). The overall 1-year survival was ~70%. Approximately half of patients survive 2 years or more, but longer follow-up is required to accurately assess OS.

Fulvestrant therapy was well tolerated. Some adverse events were noted in 18 patients (90%), but mostly grade 1–2. The most common symptom was general weakness (asthenia) – in 16 patients (80%).

Table 4. Profile toxicity fulvestrant

Unwanted phenomenon	Frequency (patients)
Any adverse events (total)	18 out of 20 (90%)
Asthenia	16 (80%)
Tides heat	5 (25%)
Head pain	4 (20%)
Nausea	4 (20%)
Local reactions on injections	0
Heavy toxicity (≥ grade 3)	0
Discontinuation of therapy due to AE	0

Hot flashes were reported by 5 patients (25%). Headache and nausea episodes occurred in 4 patients (20%) during treatment. No local reactions to injections (pain, inflammation) were registered. Other mild events were observed in isolated patients, which did not require specific treatment (Table 4). There were no cases of grade 3–4 toxicity or discontinuation of therapy due to side effects.

DISCUSSION

The results of the study demonstrated high clinical efficacy of fulvestrant in patients with metastatic breast cancer who had previously received various types of therapy. The proportion of patients who achieved disease control (PR or long-term stabilization) was 65%. This corresponds to the clinical benefit indicators (Clinical Benefit) of fulvestrant described in the literature. Thus, in the CONFIRM study, clinical benefit was achieved in approximately 64% of patients using a dose of 500 mg . Our data are also comparable with the results of domestic experience with fulvestrant : according to reports from Russian authors, stabilization or regression of the disease is observed in 50–70% of

patients with HR+ mBC during fulvestrant therapy , mainly in bones and soft tissues. The higher percentage of stabilization noted by us (55% at a threshold of ≥6 months) may be associated with the favorable profile of our patients (40% had no visceral metastases). The obtained median progression-free survival (6 months) is consistent with the results of key studies of fulvestrant . In particular, in phase III of the CONFIRM study, the median time to progression for a dose of 500 mg was 6.5 months. The one-year PFS in our observation (45%) is also close to the CONFIRM data, where about 34% of patients remained progression-free after 1 year of therapy . The slightly higher indicators in our study can be explained by the small sample size and a slightly more favorable status of patients (exclusion of HER2+ cases, some patients without visceral foci). Nevertheless, the obtained results confirm that fulvestrant provides a median disease control period of ~6 months in previously treated hormone-sensitive patients with mBC , which is a good outcome given the minimal toxicity of therapy. At the end of the follow-up, the median overall survival had not been reached, which is expected for a relatively early analysis. However, the 1-year overall survival of 70% indicates a satisfactory prognosis for patients on therapy. In the literature, the median OS with the use of fulvestrant in the second line is reported at ~2–3 years . In the CONFIRM study , the final median OS was 26.4 months (about 2.2 years) at a dose of 500 mg . Further follow-up of our cohort will likely allow us to reliably estimate this indicator; for now, it can be stated that the obtained survival indicators do not contradict the data of previous studies and fit within the prognosis for this category of patients. Of particular interest is the efficacy of fulvestrant in patients with different previous treatments. In our study, fulvestrant was successfully used both after the ineffectiveness of previous hormonal therapy (tamoxifen, aromatase inhibitors) and after chemotherapy. Despite the small sample size, it can be noted that even in patients with hormone resistance (progression on tamoxifen /AI), stabilization of the disease was often achieved on fulvestrant. This confirms the unique mechanism of action of the drug, which allows overcoming some types of endocrine resistance. It is known that fulvestrant is active after therapy with tamoxifen and aromatase inhibitors , and is also able to act in tumors with ESR1 mutation (occurring after treatment with AI). At the same time, the combination of fulvestrant with modern agents (CDK4 / 6, PI3K / AKT / mTOR inhibitors , etc.) is considered as a preferred approach in the progression of HR + mBC in women . In our practice, several patients after progression on fulvestrant were successfully treated with palbociclib + fulvestrant , which allowed them to achieve disease control again. Thus, fulvestrant fits into the multilinear strategy of mBC treatment , providing a valuable option both as monotherapy and in combinations.

In terms of safety, the data obtained confirm the favorable tolerability profile of fulvestrant . The drug did not cause serious adverse events in our patients; most of the observed symptoms (asthenia, hot flashes, headache) corresponded to the known side effects of menopausal hormone therapy and were mild. The absence of grade 3–4 toxicity correlates with the data of large studies, which note that fulvestrant does not lead to systemic side effects, except for mild estrogen-deficiency symptoms , and does not worsen the patient's quality of life . Some problem with therapy may be the need for intramuscular injections of a large volume of the drug, however, in our experience, no patient refused treatment for this reason; severe local reactions were not noted. In general, high tolerability allows for long-term treatment with fulvestrant without fear of cumulative toxicity. This is important given the chronic nature of mBC and the need for lifelong therapy. The limitations of this study include the small sample size and its retrospective nature. Nevertheless, the results add to the body of data on the use of fulvestrant in real-world clinical practice. The efficacy and survival rates obtained are consistent with the results of international clinical trials and demonstrate that fulvestrant remains a key drug for the treatment of hormone-receptor positive metastatic breast cancer.

CONCLUSION

Fulvestrant has proven itself as an effective and safe hormonal therapy for metastatic breast cancer. In the conducted analysis, the use of fulvestrant at a dose of 500 mg in patients with mBC after progression on previous treatment allowed to achieve disease control in 65% of patients, with a median time to progression of about 6 months. The therapy was well tolerated, without serious toxicity. These results confirm the feasibility of widespread use of fulvestrant in patients with luminal mBC at stages of disease progression. Given the emergence of new combinations (with CDK4/6 inhibitors, etc.), fulvestrant retains its important place in the step-

by-step treatment of mBC as the basis of endocrine therapy at advanced stages of the disease.

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