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Best Practice

Prospects of eribulin administration for patients with HR-positive HER2-negative metastatic breast cancer after progression on CDK4/6 Inhibitors: theoretical background and first experience

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Abstract

Combining cyclin-dependent kinases 4 and 6 (CDK 4/6) inhibitors with endocrine therapies in hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in the first and second lines has emerged as optimal treatment strategy and has implications related to clinical efficacy, rapid clinical response and manageable tolerability. However, approximately one in five women has progression during the first year, we have to make efforts to choose the treatments for hormone receptor-positive breast cancer. Potential treatment options include prospective chemotherapy drug eribulin, its efficacy has been demonstrated in various biological subtypes of metastatic breast cancer in patients pretreated with anthracyclines and taxanes.

Data from EMPOWER study evaluating the use of eribulin in female patients with hormone positive HER2-negative metastatic breast cancer who received CDK 4/6 inhibitor therapy showed promising results. In the cohort eribulin was prescribed according to the FDA indications in the USA after at least three prior regimens with a prior anthracycline and a taxane overall response rate was 26.7%, clinical benefit rate was 54.1%, median progressive-free survival was not reached and 6-month progressive-free survival rates was 70.4%. Eribulin demonstrated a manageable tolerability profile, adverse event rates were similar to those in clinical trials and other observational studies. In this paper we present the analysis from Russia of five cases of luminal HER2-negative breast cancer who had progression after CDK 4/6 inhibitor therapy. All patients had visceral metastases, one of them had brain metastases. Eribulin was used according to prescribing information in Russia, in metastatic settings in patients pretreated with anthracyclines and taxanes in the second chemotherapy line (3 patients) and in the third line (2 patients). Four patients achieved stable disease, one patient had partial response. Duration of eribulin treatment response was from 8 to 22 months. Eribulin appeared to be well-tolerated, dose reduction was not noted.

Data from EMPOWER (USA) and the first treatment results from Russia demonstrated eribulin may be a potential treatment option in hormone-positive breast cancer following prior CDK 4/6i therapy for disease control and to preserve quality of life.

Key words: advanced breast cancer, hormonal therapy with CDK 4/6 inhibitors, hormone resistance, eribulin chemotherapy.

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Практический опыт

Перспективы применения эрибулина у пациенток с HR+HER2-негативным метастатическим раком молочной железы после прогрессирования на CDK4/6-ингибиторах: теоретические предпосылки и первый опыт

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Аннотация
Комбинированная эндокринотерапия с CDK4/6-ингибиторами в 1–2-й линии лечения распространенного люминального HER2-негативного метастатического рака молочной железы (мРМЖ) является оптимальной лечебной стратегией, обеспечивая высокие показатели эффективности, быстроты реализации ответа и управляемого профиля токсичности. Однако уже в первый год дальнейшее прогрессирование заболевания имеет каждая 5-я пациентка; вопрос выбора дальнейшего режима лечения гормонорезистентного РМЖ становится весьма актуальным. Среди потенциальных лечебных опций весьма перспективным представляется эрибулин, как химиотерапевтический агент, показавший свою эффективность при разных биологических подтипах мРМЖ, предлеченных антрациклинами и таксанами. Первые результаты исследования EMPOWER по оценке эффективности и безопасности применения эрибулина у пациенток после прогрессирования на CDK4/6-ингибиторах в рутинной практике онкологов США показали обнадеживающие результаты. В группе пациенток, получивших лечение эрибулином по зарегистрированным в США показаниям (3-я линия химиотерапии мРМЖ после антрациклинов и таксанов), объективный ответ имели 26,7%, а клиническую эффективность – 54,1% больных, медиана выживаемости без прогрессирования не была достигнута, а показатели 6-месячной выживаемости без прогрессирования составили 70,4%. Профиль безопасности терапии был благоприятным и соответствовал ранее проводимым исследованиям. Нами был проанализирован опыт применения эрибулина у 5 российских пациенток с люминальным HER2-негативным мРМЖ после прогрессирования на комбинированной эндокринотерапии с CDK4/6-ингибиторами. Все пациентки имели висцеральное метастазирование, в одном случае – поражение центральной нервной системы. Эрибулин применялся в соответствии с рекомендациями, зарегистрированными на территории Российской Федерации, на этапе метастатической болезни после полученных ранее антрациклинов и таксанов в качестве 2-й линии (у 3 пациенток) и 3-й линии химиотерапии (у 2 больных). Стабилизация опухолевого процесса достигнута у 4 пациенток, частичный ответ – в 1 случае; продолжительность ответа на терапию эрибулином составила 8–22 мес. Отмечен благоприятный профиль безопасности терапии, редукция дозы не проводилась. Опыт коллег США и первые результаты лечения российских больных показывают, что химиотерапия эрибулином может оказаться весьма успешной при гормонорезистентном РМЖ, что позволит иметь длительный контроль над проявлениями заболевания и хорошее качество жизни.
Ключевые слова: распространенный рак молочной железы, комбинированная эндокринотерапия с CDK4/6-ингибиторами, гормонорезистентность, химиотерапия эрибулином.
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Breast cancer is the most common oncopathology in the incidence of disease and mortality in women around the world [1]. Despite the available modern treatment based on biological characteristics of the tumor, about 25–30% of patients with early stages have further progression of the disease. In addition to that, 8% of Russian patients are diagnosed with primary metastatic cancer, which creates a high urgency for searching for effective therapy regiments for advanced stages of the disease [2, 3]. At the same time the majority of patients have a hormone positive (HR-positive) HER2-negative metastatic breast cancer where estrogen/progesterone receptors (the biologically justified targets for the current antitumor action) are expressed in the tumor [4, 5].

Current HR-positive HER2-negative metastatic breast cancer treatment principles

Studies of the last decade have shown that the survival rate of patients with luminal HER2-negative metastatic breast cancer receiving endocrine therapy is comparable to that of primary chemotherapy [6]. Specifically, the median progression-free survival rate (PFS) is 6 months for endocrine therapy with tamoxifen, 9–14 months for the therapy with aromatase inhibitors (AI), and almost 17 months for the therapy with fulvestrant [4]. The maximum efficacy has been witnessed in patients with nonvisceral metastases whose PFS median for the therapy with fulvestrant reached 23.3 months [7]. In addition to the above, the risk-benefit profile and the quality of life in patients receiving endocrine therapy remain very high throughout the treatment.

The emergence of a new class of CDK4/6 inhibitors drugs (palbociclib, ribociclib, abemaciclib) has revolutionized the treatment of advanced hormone positive HER2-negative breast cancer demonstrating the perfect combination of high treatment effect, speed of response, and controlled toxicity profile.

The efficacy of CDK4/6 inhibitors as the first-line treatment of HR-positive HER2-negative metastatic breast cancer was convincingly demonstrated in five randomized Phase II–III studies (PALOMA-1/2, MONALEESA-2/3/7). There was a significant increase in the PFS median in the groups with CDK4/6 inhibitors of up to 20–37 months, which means an additional 9–14 months of life without disease progression in comparison with the control group . It is extremely important that these results have been confirmed in visceral metastases as well as in premenopausal patients [8–13]. A significant increase in the overall survival rate (OS) for ribociclib and abemaciclib was confirmed in 2019. So, in Phase III of the MONALEESA-7 study, 70.2% of premenopausal patients remained alive throughout the 42-month follow-up median in the ribociclib group versus 42% of patients in the group without ribociclib, the risk of death decreased by 29% (HR 0.712, p=0.009) [14].

The use of CDK4/6 inhibitor combinations with fulvestrant as a second line therapy after progression on AI therapy was analyzed in three major randomized Phase III studies (PALOMA-3, MONALEESA-3, MONARCH-2). The differences in the PFS median compared to the monotherapy with fulvestrant are quite significant: 9.5 vs 4.6 months, Δ 4.9 months – for the combination with palbociclib (95% CI 0.40–0.62); 14.6 vs 9.1 months, Δ 5.5 months – for the combination with ribociclib (95% CI, 0.443–0.737); 16.4 vs 9.3 months, Δ 7.1 months – for the combination with abemaciclib (95% CI, 0.449–0.681) [15]. Just like for ribociclib, the combination of abemaciclib with fulvestrant as the second line therapy confirmed its advantage in OS in 2019: 46.7 vs 37.3 months compared with fulvestrant, HR 0.757, p=0.01 [16].

The results of these studies formed the basis for HR-positive HER2-negative metastatic breast cancer treatment guidelines, which emphasize that endocrinotherapy is the leading treatment option in the absence of visceral crisis and signs of hormone resistance, and the combinations with CDK4/6 inhibitors (palbociclib, ribociclib or abemaciclib) are given priority as a first and second line therapy [17, 18].

Despite the high efficacy of this class of drugs, already in the first year of combined therapy with CDK4/6 inhibitors every fifth patient has a further progression of the disease. The que-

stion of choosing the further strategy (to maintain endocrinotherapy or to start chemotherapy) becomes a difficult one. Lack of results of studies with randomized assignment on maintaining of endocrinotherapy after disease progression (including maintaining/change of the CDK4/6 inhibitors), as well as lack of understanding of the biological mechanisms of hormone resistance development leads to the fact that oncologists often prefer a subsequent chemotherapy. So, according to N. Princic et al., in 35.6% of patients in the USA with HR-positive HER2-negative metastatic breast cancer with progression on CDK4/6 inhibitors oncologists prescribed a subsequent chemotherapy [19]. The choice of a cytostatic agent for a subsequent therapy is determined not only by its potential efficacy in pretreated patients, but also by the safety profile of the therapy. Eribulin as a chemotherapeutic agent, which has shown its effectiveness in various biological subtypes of metastatic breast cancer in patients pretreated with anthracyclines and taxane, may be promising as possible subsequent treatment options.

Eribulin in the metastatic breast cancer treatment: antitumor activity mechanism and results of efficiency against HER2-negative breast cancer

Eribulin is a microtubule polymerization inhibitor, a synthetic analogue of Halichondrin B, which possesses multiple mechanisms of antitumor activity realization. The drug blocks tumor-cell division by forming functionally inactive tubulin units, reducing the rate and degree of polymerization of the tubulin, disrupting the formation of mitotic spindle, causing an arrest of tumor cells in the G2-M cell cycle phase, and stimulation of apoptosis [21]. The non-mitotic mechanisms of the eribulin action (tumor vascular bed remodeling, reversion of epithelial-mesenchymal transition, and decrease in the ability of tumor cells to migrate and invade) are unique [20, 21]. The efficacy of eribulin in patients with metastatic breast cancer with the progression under a therapy with anthracyclines and taxanes was shown in Phase III EMBRACE study with randomized assignment. The drug demonstrated a significant increase of the OS median (13.2 vs 10.5 months, p=0.014) in patients who received at least two lines of treatment, compared to the therapy chosen by a doctor [22]. According to the published in 2018 results of subset analysis of the randomized 301 study an increase in the OS median in the eribulin group was indicated in comparison with capecitabine in patients with HER2-negative metastatic breast cancer in the 2nd line of the therapy (16.1 vs 13.5 months, p=0.026) [23, 24]. Therefore, to date, eribulin is a drug that has shown efficacy against HER2-negative breast cancer starting from the second line therapy of the advanced disease, which explains the interest in studying the potential of its use in patients with the progression under CDK4/6 inhibitors.

Prospects of eribulin use for patients with HR-positive HER2-negative metastatic breast cancer after CDK4/6 inhibitors progression (EMPOWER study results)

In 2019, the results of a major American observational study EMPOWER were presented, which analyzed the efficacy and safety of the eribulin use in patients with the progression under a treatment with CDK4/6 inhibitors [25]. The data for the study were collected from a U.S. national database that included patients treated between February 2015 and December 2017. The analysis included 395 patients with HR-positive HER2-negative metastatic breast cancer, 63.5% of whom had a primary metastatic breast cancer, and CDK4/6 inhibitors were prescribed as the first– and second-line treatment in 71.7 and 18.0% of the patients, respectively. Most patients received palbociclib (88.4%) in combination with letrozole (47.9%), fulvestrant (29.4%) or other endocrine partners (11.1%); ribociclib (6.8%) or abemaciclib (3.5%) was significantly less frequently used. The median duration of response to a therapy with CDK4/6 inhibitors was 9.7 months, the median of follow-up from the beginning of the first line therapy was 12.4 months.

The patients were divided into 4 cohorts according to the eribulin administration:

1) eribulin was used as the second line therapy, 121 (30.6%) patients (directly following discontinuation of CDK 4/6 inhibitors);

2) eribulin was prescribed as the third line, 111 (28.1%) patients after at least three prior regimens but with a prior anthracycline and a taxane;

3) eribulin was prescribed according to the FDA indications in the USA, 135 (34.2%) cases;

4) eribulin was used in the fourth line therapy, but without a prior therapy with anthracyclines and taxanes, 28 (7.1%) patients.

There were 135 patients in cohort with patients received eribulin according to the established indications for use in the USA (3L after at least two chemotherapeutic regimens with a prior therapy with anthracyclines and taxanes for the metastatic stage). The median age of patients was 64.3 years, 92.6% of the patients had visceral metastases (including 51.9% with liver metastases and 56.3% with lung metastases) and 6.7% were diagnosed with brain metastases [25]. Efficacy on the tumour shrinkage was observed in 87 (64.4%) patients, the rate of objective (partial) response was in 36 (26.7%) patients. The clinical efficacy (partial response + stabilization of disease) was in 73 (54,1%) patients and a progression was in 14 (10.4%) patients. At the beginning of the analysis clinical response was not estimated in 48 (35,6%) patients. The PFS median was not reached, 6-month PFS was 70.4%,

The safety profile of the eribulin therapy was well tolerated, neutropenia was observed in 23% of the cases (febrile neutropenia was observed in 0.7% of the patients only), peripheral neuropathy was noted in 11.1% of the cases and diarrhea – in 12.6% of the cases. CSF support was in 11.9% patients during eribulin treatment.

Therefore, the first first experience of eribulin therapy in patients with HR-positive HER2-negative metastatic breast cancer after the progression on combined endocrine therapy with CDK4/6 inhibitors in the USA showed good efficacy and favorable safety profile of the therapy. Of course, the final conclusions of this study are still to be drawn in the future when it will be possible to evaluatethe efficacy of the treatment in all the patients included in the study and when follow-up time will be enough for a correct analysis. However, it is already evident that the combination of the unique spectrum of antitumor activity and the safety of the therapy makes eribulin a promising potential treatment option for patients with hormone-resistant metastasis breast cancer after CDK4/6 inhibitors progression.

The greatest interest is the clinical experience of eribulin administration to Russian patients with HR-positive HER2-negative metastatic breast cancer after its progression on combined therapy with CDK4/6 inhibitors; the experience is still limited, but quite revealing.

Initial results of eribulin use for Russian patients with HR-positive HER2-negative metastatic breast cancer after CDK4/6 inhibitors progression.

Clinical case 1

Clinical information and anamnesis: A 41-year-old female patient, treatment for a right breast cancer stage T2N1M0 (invasive lobular carcinoma, luminal HER2-negative subtype) in 2001 included: radical mastectomy, adjuvant chemotherapy (4×CAF, paclitaxel), adjuvant radiation therapy on the chest wall and the lymph nodes, X-ray ovarian suppression, adjuvant endocrine therapy with tamoxifen for 5 years.

The therapy after progression: since 2012 (lung metastases): the 1st line of chemotherapy (6×CAF), partial response, the 1st line of endocrinotherapy (anastrozole, from April 2013 to June 2014).

In June 2014 was found lung and mediastinal lymph node metastases, pleurisy. Biopsy of the mediastinal lymph nodes was made breast cancer metastases was verified, ER Immunohistochemical (IHC) Allred score – 8, PR – 8, HER2-0 Ki67–80%. Patient received endocrine therapy under the framework of the PALOMA-3 protocol: 35 courses of 500 mg fulvestrant: once per 28 days + 125 mg palbociclib/placebo – once per 21 days. The effect was estimated as partial response. Treatment was until March 2017.

Since September 2017 (mediastinal lymph nodes metastases growth) – the 2nd line of chemotherapy: paclitaxel + carboplatin, 6 cycles, partial response.

Since April 2018 (bone metastases) – 4th line of endocrine therapy with fulvestrant and bisphosphonates infusion with stabilization.

In September 2018 was found new progression (metastases in the supraclavicular lymph nodes, liver, bones, omentum, lungs, pleura), patient received eribulin therapy (3rd line of chemotherapy) in dose 1.4 mg/m² on days 1, 8 of the 21-day cycle + administration of bisphosphonates. Disease stabilization achieved, duration of response – 12 month. Fig. 1. The treatment is ongoing, the tolerability is favorable, no adverse events have been observed, without the dose reduction.

Clinical case 2

Clinical information and anamnesis: a 27-year-old female patient, in 2017 received a treatment of a left breast cancer stage T2N1M0 (invasive ductal carcinoma, luminal HER2– negative subtype, Ki67–45%, BRCA-negative status): neoadjuvant chemotherapy 4AC-12 × weekly paclitaxel 80 mg/m² followed by a radical mastectomy. According to morphological data: residual breast carcinioma ypT2(m) ypN1c G3, , metastases in 3 lymph nodes. The IHC of the residual tumor: ER – IHC Allred score 8, PR – 6, HER2– 1+, Ki-67– 65%. Adjuvant radiation therapy was carried out. Since December 2017, AI were started with ovarian suppression (goserelin)

The therapy after progression: since July 2018 (multiple bone metastases) patient received the 1st line of endocrine therapy (fulvestrant + palbociclib and a concurrent goserelin administration), L3 vertebroplasty and bisphosphonate infusion. It resulted in stabilization.

Since December 2018 (lung and mediastinal lymph node metastases, reinforcement of the lytic component in the bones) – the 1st line of chemotherapy with capecitabine, radiation therapy for areas of lytic bone metastases

In February 2019, the MRI revealed the frontal bone affection, with subcutaneous permeation to the depth of 1.1 cm and intracranial permeation to 2.1 cm – the mass lesion with signs of diffusion restriction, with the dimension of up to 3.5×3.8×3.8 cm. A similar formation was identified in the left frontal pole with the dimension of 2.2×2.0×2.15 cm and in the right frontal bone of up to 1.1×1.5 cm, as well as the inhomogeneous MR signal locus in the right parietal bone up to 0.8 cm in diameter. The lesion of cerebral membranes of up to 6.2 cm long and 1.4 cm thick was noted (Fig. 2).

Eribulin therapy (2nd L of chemotherapy) started since February 2019 in dose – 1.4 mg/m² on days 1, 8 days of the 21-day cycle + bisphosphonates infusion, 10 cycles in total. The effect was partial respone (decrease in the intracranial lesions) and stabilization in the bone lesions and mediastinal lymph nodes; Fig. 2. The duration of the response was 8 months, a significant improvement in the quality of life was noted. The tolerance of chemotherapy with eribulin was satisfactory, neutropenia grade 1–2 and anemia grade 1 were noted. No dose reduction was required.

Clinical case 3

Clinical information and anamnesis: in 2016, a 54-year-old female patient in menopause underwent a treatment for a right breast cancer stage T1cN0M0 (luminal HER2-negative subtype) which included breast– conserving surgery, adjuvant chemotherapy (4 × AC cycles), adjuvant radiation therapy for the breast, adjuvant endocrinotherapy with anastrozole (December 2016 – October 2017).

The therapy after progression: since October 2017 (liver and bone metastase) patient received the 1st line of chemotherapy (8 cycles of docetaxel + carboplatin), bisphosphonates infusion , with a partial response, the 1st line of endocrinotherapy (exemestane , from April 2018 to August 2018).

Since August 2018 to December 2018 (growth of lesions in the liver) recieved the 2nd line of endocrinotherapy with CDK4/6 inhibitors (palbociclib + letrozole), with a negative dynamics in liver.

Eribulin (2nd L of chemotherapy): since December 2018 received eribulin in dose 1.4 mg/m2 on days 1, 8 days of the 21-day cycle, 13 cycles in total, with stabilization of the disease. Duration of the response – 10 months, tolerance of therapy with eribulin was favorable, no adverse events were noted, without the dose reduction.

Fig. 1. The efficacy of eribulin as the 3rd line of chemotherapy in a patient with HR-positive HER2-negative metastatic breast cancer, before the start of an eribulin therapy and after 11 months of the therapy.
Рис. 1. Эффективность эрибулина в качестве 3-й линии химиотерапии у пациентки с HR+HER2-негативным распространенным раком молочной железы. Стрелками указаны контрольные очаги до начала терапии эрибулином и спустя 11 мес лечения.

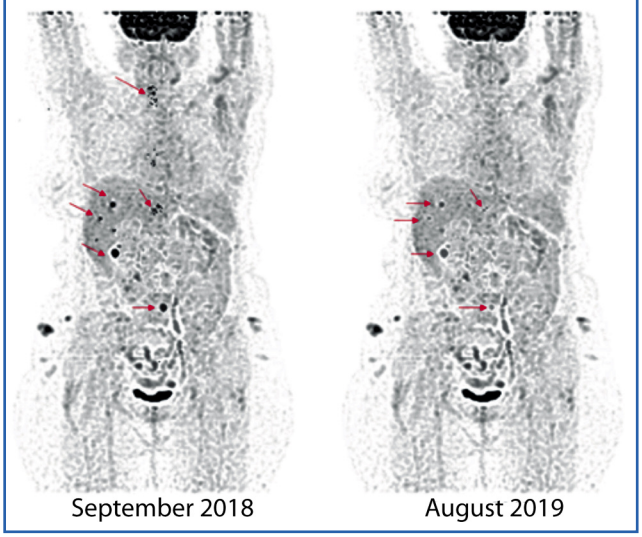
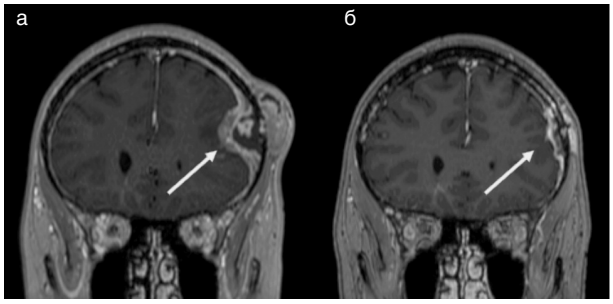


Fig. 2. Metastases in the frontal bone, cerebral membranes with intracranial component (*a* – before the eribulin therapy, *b* – after 10 cycles of eribulin).
Рис. 2. Метастатическое поражение лобной кости, мозговых оболочек с интракраниальным компонентом: *а* – до лечения эрибулином; *б* – после 10 введений эрибулина.



Clinical case 4

Clinical information and anamnesis: a 57-year-old female patient, in 2011 was found right breast cancer stage T4N2M1 (liver metastases, luminal HER2-negative subtype), patient received sanitary mastectomy , 15 cycles of chemotherapy (docetaxel, cyclophosphamide) and 5 cycles of chemoembolization of the liver metastases with doxorubicin, with a partial response. From 2011 to 2016, the 1st line of endocrinotherapy (letrozole) was administered; the effect of stabilization was obtained.

In January 2017, a resection of right lung was performed due to solitary breast cancer metastases, followed by endocrinotherapy with AI.

In August 2018 was found a progression (liver metastases; biopsy was made and confirmed of the breast cancer metastasis, ER – IHC Allred score 4, PR – 0, HER2-0 Ki67 – 15%). From August 2018 to December 2018 received the 2nd line of endocrinotherapy (palbociclib + fulvestrant). In December 2018, a negative dynamics of liver metastases was noted.

Eribulin therapy (2nd L of chemotherapy): was started in dose1.4 mg/m2 on days 1, 8 of the 21-day cycle, the effect of the treatment – stabilization. The duration of the response was 12 months, a neutropenia grade 2 was observed after the 2nd cycle (administration was suspended), no further adverse events were observed, without the dose reduction.

Clinical case 5

Clinical information and anamnesis: a 47-year-old female patient. In 2004–2005, a treatment for a right breast cancer stage T1N0M0

Efficacy and safety of the eribulin therapy in Russian patients with HR-positive HER2-negative metastatic breast cancer after CDK4/6 inhibitors progression
Эффективность и безопасность терапии эрибулином у российских больных с HR+HER2-негативным метастатическим раком молочной железы (мРМЖ) после прогрессирования на CDK4/6-ингибиторах

Clinical case	Age	Metastases site prior to eribulin therapy	Prior endocrinotherapy for metastatic breast cancer	Prior chemotherapy (including adjuvant regimens)	Line of chemotherapy with eribulin	Efficacy of eribulin therapy	Duration of response to eribulin therapy, months	Adverse event	Eribulin dose reduction
1	41	Lymph nodes, liver, bones, lungs, pleura, omentum	Anastrozol, Fulvestrant + palbociclib/placebo, Aromasin, Fulvestrant	CAF, Paclitaxel + carboplatin	3rd	Stabilization	12	Not observed	None
2	27	Bones, mediastinal lymph nodes, cerebrum	Palbociclib + fulvestrant	AC – paclitaxel (adjuvant chemotherapy), Capecitabine	2nd	Partial response (intracranial metastasis)	8	Neutropenia grade ½ anemia grade 1	None
3	54	Liver, bones	Exemestane, Palbociclib + letrozole	AC (adjuvant chemotherapy), Docetaxel + carboplatin	2nd	Stabilization	10	Not observed	None
4	57	Lungs, liver	Letrozole, Palbociclib + fulvestrant	Docetaxel + cyclophosphan, Doxorubicin (intra-arterial)	2nd	Stabilization	12	Neutropenia grade 2	None
5	47	Lungs, intra-abdominal metastases	Anastrozol, Fulvestrant, Palbociclib + fulvestrant, Everolimus + Exemestane	CAF (adjuvant chemotherapy), Paclitaxel + carboplatin, Docetaxel + cyclophosphan	3rd	Partial response	22	Not observed	None

was performed (breast-conserving surgery, adjuvant chemotherapy (6 x FAC), adjuvant radiation therapy, endocrine therapy with tamoxifen and AI. According to the morphological examination – invasive lobular G3 carcinoma of the luminal HER2-negative subtype.

The therapy after progression: in 2013, a tumor mass was detected in the iliac region, a panhysterectomy with iliac lymph node dissection, omentectomy, appendectomy, nephrostomy on the right, at the morphological examination – metastases of lobular breast cancer, ER – IHC Allred score 8, PR – 8, HER2 – 0. The 1st line of endocrinotherapy (anastrozole) from February 2014 to May 2015 was carried out.

Since March 2015 (intraperitoneal dissemination) the 1st line of chemotherapy was carried out (paclitaxel + carboplatin, 3 cycles), with progression.

From June 2015 to March 2016 – the 2nd line of endocrinotherapy (fulvestrant), resulted in a stabilization effect.

Since March 2016 (intra-abdominal dissemination) – the 2nd line of chemotherapy with docetaxel + cyclophosphamide, with progression.

From May 2016 to June 2017 – the 3rd line of endocrinotherapy with palbociclib + fulvestrant (under the accessibility program), with a partial effect. The therapy was discontinued due to social reasons.

From September 2017 to December 2017 the 4th line of endocrinotherapy (exemestane + everolimus), progression (intra-abdominal permeation, intestinal obstruction).

On December 2017 – transverse colostomy, at the morphological examination – metastasis of lobular breast carcinoma, ER – IHC Allred score 4, PR – 5, HER2 – 1+. At the additional examination – the appearance of metastases in the lungs, infiltration into the small pelvis with compression of the left ureter, performed nephrostomy on the left.

Eribulin therapy (3rd L of chemotherapy) since February 2018 was started eribulin in dose 1.4 mg/m2 on days 1, 8 of the 21-day cycle, 29 cycles of chemotherapy in total. The effect was a partial regression. Duration of the response – 22 months, tolerability of the therapy was satisfactory, no adverse events were observed, without reduction of the dose.

Consideration of the eribulin therapy responses and conclusions

The treatment response of Russian female patients are summarized in Table. As can be seen from the data presented, all the patients received endocrine therapy for the metastatic stage (one to four lines of therapy), including combinations with CDK4/6 inhibitors (palbociclib), before the beginning of the eribulin therapy. Patients had different areas of metastases, , including liver, lungs, mediastinal lymph nodes, bones, intra-abdominal metastases and even central nervous system affliction.

Eribulin was used according to recommendations registered in the Russian Federation at the metastatic disease stage after previously administered anthracyclines and taxanes as the second line (in three patients) and the third line of chemotherapy (in two patients). Despite the pre-treatment of the patients, the efficacy of eribulin was high, the stabilization of the disease (in four cases) and a partial response (in one patient) were achieved, the duration of response to the therapy with eribulin was 8–22 months. At the same time, a favorable therapy safety profile was witnessed, adverse events were observed in two cases only (in one patient – neutropenia grade 1/2 and anemia grade 1, in one another patient – neutropenia grade 2, after a break treatment was restored). There was no dose reduction.

Thus, the problem of the choice of further therapy in patients with HR+HER2– negative breast cancer after progression on CDK4/6 inhibitors becomes a difficult task in clinical practice. The first results of eribulin chemotherapy in Russian patients with hormone-resistant breast cancer demonstrate the potential for long-term control of the manifestations of the disease and a good quality of life, further experience is needed.

Conflict of interests. The authors declare that there is not conflict of interests.

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