DOI: 10.17650/1994-4098-2021-17-3-00-00

10 years of success achieved by eribulin while treating HER2-negative mBC: from randomized studies to routine practice

I.V. Kolyadina

Russian Medical Academy of Postgraduate Education, Ministry of Health of Russia; 2/1 Barrikadnaya St., Moscow 125993, Russia; V.I. Kulakov National Medical Research Center of Obstetrics, Gynecology, and Perinatology, Ministry of Health of Russia; 4 Akademika Oparina St., Moscow 117198, Russia

Contacts: Irina Vladimirovna Kolyadina *irinakolyadina@yandex.com*

The article reviews studies evaluating the efficacy and safety of eribulin chemotherapy in patients with HER2-negative advanced breast cancer. It analyzes the results derived from large randomized studies, highlights the main advantages peculiar to eribulin, and describes the key mechanisms of the antitumor activity displayed by the drug. Among those presented, there are significant retrospective studies evaluating the role of eribulin chemotherapy in late and early advanced breast cancer treatment lines, as well as an analysis of surveys aimed to evaluate the efficacy of the drug in various clinical settings (for visceral metastases, brain lesion, and in elderly patients). This article reflects the main results of Russian population analyses evaluating the efficacy and safety of eribulin chemotherapy in routine clinical practice.

Key words: metastatic breast cancer, late-line chemotherapy, early-line chemotherapy, eribulin, visceral metastases, brain metastases, chemotherapy in elderly patients, Russian experience of using eribulin, eribulin introduced after CDK4/6 inhibitors

For citation: Kolyadina I.V. 10 years of success achieved by eribulin while treating HER2-negative mBC: from randomized studies to routine practice. Opukholi zhenskoy reproduktivnoy systemy = Tumors of female reproductive system 2021;17(3): 00–00. (In Russ.). DOI: 10.17650/1994-4098-2021-17-3-00-00.

Background

Breast cancer (BC) is the leading oncopathology in women all over the world; it makes the maximum contribution not only to the cancer incidence structure, but also to the cancer mortality structure [1]. The developing resistance to drugs (both endocrine therapy and chemotherapy) appears to be the most urgent problem in modern oncology, and the search for effective antitumor drugs that show their potential in patients with pretreated advanced breast cancer (mBC) is extremely relevant and timely.

Eribulin isa microtubule polymerization inhibitor, a synthetic analogue of halichondrin B, approved for the treatment of mBC resistant to anthracyclines and taxanes [2–4]. According to the results derived from EMBRACE, a large, randomized phase III study, the drug has proved to be effective in patients with a history of two to five previous chemotherapy lines for mBC. When compared to the therapy of physician's choice, the use of eribulin demonstrates the possibility to significantly increase the patients' overall survival (OS) and reduce the death risk by 19 % (13.2 vs 10.5 months, hazard ratio (HR) 0.81, $p = 0.01$) [5].

The results of the second large randomized study (E7389-G000-301) confirmed the superiority of eribulin chemotherapy over capecitabine in mBC patients resistant to anthracyclines and taxanes; the median OS was 15.9 vs 14.5 months, HR 0.88, $p = 0.056$ [6]. This study included 1.102 mBC patients with a history of a prior therapy with anthracyclines and taxanes (≤3 prior chemotherapy lines); moreover, 15 % of patients had the HER2+ subtype. To neutralize the effect exerted on the OS by the anti-HER2 therapy, an additional analysis of Study 301 took place; it included only patients with a HER2-negative tumor subtype who received eribulin at the standard dose of 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle ($n = 186$), or capecitabine at a dose of 1.250 mg/m^2 on days 1–14 every 3 weeks ($n = 206$) as a second-line mBC therapy. A significant advantage of eribulin over capecitabine in increasing the median OS – 16.1 vs 13.5 months, HR 0.77, $p = 0.026$ – resulted from the additional analysis; at the same time, the therapy safety profile was highly favorable with both studied treatment regimens [7]. Based on the convincing results of those studies, eribulin was approved to treat anthracycline- and

taxane-resistant mBC and took its rightful place in the treatment algorithm for the advanced stage of the disease.

Antitumor action mechanisms and factors predicting high efficacy of eribulin in mBC

By its structure, eribulin isa synthetic analogue of halichondrin B obtained from the marine sponge *Halichondria okadai* [2]. The drug is characterized by its multifaceted antitumor activity: the cell cycle stops due to the irreversible blockade of tubulin microtubules with eribulin and the formation of functionally inactive tubulin aggregates [8]. In addition, the drug is known to demonstrate unique non-mitotic mechanisms of action, namely, to remodel the tumor vascular bed, reverse the epithelial-mesenchymal transition, and decrease the ability of tumor cells to migrate and invade. As it appears from the laboratory studies, a single eribulin injection resulted in improved tumor perfusion and increased microvascular network density over the next 5 days; a decrease in hypoxia suppressed genes involved in tumor signaling cascades induced by hypoxia [8–10]. Moreover, an improvement in tumor perfusion led to a greater antitumor activity of cytostatics (including those used after eribulin) [8–10]. In the course of eribulin therapy, tumor cells lost their aggressive characteristics due to the effect exerted by the drug on the reversion of the epithelial-mesenchymal mechanism by suppressing the activity of genes involved in the process [11, 12].

In 2020, Japanese authors presented the results derived froma clinical study of the eribulin effect on the metastasis nature in patients with mBC [13]. 66 patients received chemotherapy with eribulin ata standard dose of 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle: 25.8 % took the drug as the first-line therapy, 27.2 % – as the second-line, and 47 % – as the third and later therapy lines. The patients' age was 35–80 years (median – 54 years); 65.2 % had luminal HER2-negative cancer; 25.8 % of patients had a triple-negative subtype; the dominant metastasis sites included liver (57.6 %), lungs (53 %), and bones (43.9 %); brain lesion was diagnosed in 19.7 % of patients. The authors compared the progression nature (the appearance of new lesions or an increase in the size of the existing ones) before starting the eribulin therapy with the type of progression that developed during the drug therapy. On eribulin therapy, a twofold reduction was registered in the appearance of new lesion (from 49 to 25 %), both in patients with luminal cancer – from 43.8 to 21.6 %, and with the triple-negative subtype – from 75 to 29.4 %, p <0.05. The main progression characteristic in the patients receiving eribulin chemotherapy was an increase in the size of the existing lesions (from 51 to 75 %). According to the authors, this study practically confirms the phenomenon expressed in the reversion of the epithelial-mesenchymal transition to eribulin therapy and manifested in the loss of the ability to actively invade and metastasize peculiar to the tumor [13].

Owing to the accumulated experience of eribulin use in routine practice, a respective analysis took place with the aim to study the retrospective data evaluating the efficacy and safety of eribulin chemotherapy in various clinical settings with a significant part where of not considered in the framework of registration randomized studies. Despite the fact that the retrospective data are not randomized, the positive population experience in the drug use appears to be extremely valuable.

Eribulin efficacy in late-line mBC treatment: results from real-world data

A series of retrospective population studies evaluated the efficacy and safety of eribulin during the late-line treatment in patients with a history of at least 3 mBC chemotherapy lines. It seems notably difficult to choose a therapeutic regimen in these clinical settings; the accumulation of resistant tumor clones makes each subsequent treatment line less effective, and the deteriorating patient's somatic status reduces the therapy reserves still more. That is why the choice of a cytostatic agent that combines antitumor activity and a favorable safety profile is highly demanded.

TROTTER, a multicenter retrospective study, evaluated the eribulin efficacy in 113 patients with mBC who received treatment in 10 Italian clinics [14]. The patients' median age was 62 years; 71.7 % had visceral metastases; the median of previous chemotherapy lines before introducing eribulin was 3 (1–10). Despite the patients' significant pre-treatment, the objective response rate to eribulin therapy was 24 % with the clinical benefit rate reaching 35.4 %. With a median follow-up of 29.6 months, the median progression-free survival (PFS) amounted to 3.3 months, and the median OS was 11.6 months. As the authors note, the eribulin chemotherapy efficacy did not depend on the biological subtype of BC, metastasis sites, or previous therapy lines, and the treatment safety profile appeared to be highly acceptable: grade 3–4 adverse events included the development of neutropenia (19.4 %), asthenia (3.5 %), and increased liver enzymes (1.8 %); febrile neutropenia was registered in only 0.9 % of cases [14].

Another large retrospective Italian study, ESEMPiO, included 497 patients from 39 Italian centers; the median age was 54.5 years (24–79 years) [15]. In the structure of biological subtypes, hormone-positive cancer prevailed (79.9 %), 13 % of patients had a triple-negative subtype, and 7.1 % – HER2+ mBC. The median of the previous chemotherapy lines for advanced stage reached 5; eribulin was prescribed as the third line in only 13.1 % of patients, as the fourth line – in 19.3 %, and ≥5 lines – in 60.4 % of cases. The median of the performed eribulin therapy cycles was 4 (1–20). When eribulin was prescribed in the third line, the median OS reached 12.6 months, in the fourth line – 11.5 months, and amounted to 9.7 months with the drug prescription as ≥5 treatment line. The authors note a favorable safety profile of eribulin treatment;

chemotherapy discontinuation due to toxicity was rare (only 9.2 % of cases) [15].

A large multicenter retrospective study with 272 patients receiving eribulin chemotherapy from November 2019 to October 2020 at 9 institutes in China was presented in 2021 [16]. The median of chemotherapy lines prior to eribulin was 4 (2–5); 94.9 % of patients had previously received taxanes, 82.7 % – anthracyclines. The patients' median age was 52 years (28–78); 90 % of cases exhibited recurrent BC; luminal HER2-negative and triple-negative subtypes were diagnosed in 55.5 and 32.7 % of cases, respectively. Visceral metastases dominated (79.4 %) and included liver (51.8 %) and lung (47.4 %) lesions; 55.1 % of patients had lesions of three areas or more. The median PFS amounted to 4.1 months; the objective response rate was 17.6 % with clinical efficacy of 24.6 %; the disease stabilization was noted in 44.1 % of cases. Among the predictive factors, the authors identified the number of metastatic sites (1–2 vs ≥3 – median PFS 5.3 vs 3.6 months, respectively, $p = 0.023$), as well as prior taxane therapy ≥6 vs <6 months before starting the eribulin therapy (median PFS – 6.5 vs 3.7 months, $p = 0.048$). The therapy safety profile appeared to be highly favorable: the most common grade 3–4 adverse events included neutropenia (18 %), leukopenia (5.5 %), and anemia (1.1 %); neuropathy cases were rare (only 1.1 %); eribulin dose reduction was required in only 7 % of cases [16].

Thus, eribulin in late-line mBC treatment demonstrates a good balance between the efficacy and safety of the therapy. Despite the pre-treatment received by patients, chemotherapy with eribulin makes it possible to obtain an objective response in 20–25 %, delay the time to subsequent progression (median PFS up to 4.0 months), and prolong the patients' life (median OS about 1 year) while maintaining its quality.

Eribulin efficacy in early-line mBC treatment: results from real-world data

Due to a good balance between the antitumor activity and safety of the therapy, as well as the eribulin efficacy regardless of the biological subtype of the tumor and metastasis sites, the experience in the drug use in earlier lines of treatment for mBC has been accumulated actively.

VESPRY, a multicenter observational study, addressed the eribulin efficacy in 118 patients with mBC as a third-line therapy [17]; the median age of women was 58 years while the median of eribulin cycles performed was 5.5 (1–26). According to the authors, the drug proved to be highly effective in all clinical settings. The median PFS was 5.5 months in the general group, 5.2 months in the subgroup of patients with triple-negative cancer, 6.1 months in patients over 65, and 5.5 months in patients with visceral lesions. The maximum level of objective responses was recorded with central nervous system lesions (16 %) and liver metastases (14.9 %) [17].

Of particular interest are the results obtained froma retrospective study TETRIS with the inclusion of 44 patients with triple-negative subtype mBC; the treatment with eribulin as a second-line chemotherapy for an advanced stage took place from January 2013 to September 2019 in 14 centers in Italy [18]. The patients' median age was 51 years; 50 % of patients had visceral metastases, 71 % had ≥2 metastasis sites. In 89 % of women, recurrent BC was observed; previous chemotherapy (neo/adjuvant treatment or first-line therapy of mBC) included taxanes (86 %), anthracyclines (61 %), carboplatin (32 %), and capecitabine (14 %); in 43 and 27 % of cases, two- and three-component combinations of cytostatics were used. As follows from the authors' data, the median PFS with the previous first-line chemotherapy amounted to 7 months, and with eribulin therapy as a second line – 3.5 months; 1-year PFS was 16.7 %. The median OS was 11.9 months, 43 % and 12.7 % survived one and two years, respectively. 18.2 % of patients had a partial response to eribulin therapy; stabilization was recorded in 22.7 % of cases. It was noted that patients with a long-term response to the previous (first) line of chemotherapy for mBC (time to progression >10 months) had a good response to eribulin therapy (43 % of cases showed PFS >12 months). At the same time, the duration of the response to the first-line treatment before introducing eribulin (more than 6 months vs less than 6 months) significantly correlated with OS: 1-year OS was 58.7 vs 26.8 %, and 2-year OS was 14 vs 8.9 % in favor of patients with a long-term response to the previous treatment, $p = 0.02$. In addition, at the time of initiating the eribulin therapy, the ECOG status was found to be the second significant predictive factor: 1- and 2-year OS reached 63.6 % and 27.3 % (the ECOG status – 0) vs 26.7 % and 0 % (the ECOG status – 1–2), $p = 0.003$ [18].

In 2021, S. Mougalian et al. presented a major experience in the use of eribulin as early-line treatment; the analysis included 513 women with mBC who received eribulin treatment in the United States from January 2011 to December 2017 [19]. The patients' median age was 59 years; the ECOG status – 0–1 (61 %), 57 and 67 % had liver and lung lesions, respectively, 4.3 % had brain metastases; triple-negative cancer was diagnosed in 49.9 % of patients. Eribulin was prescribed as a third-line chemotherapy for mBC in 78 % of cases; the median therapy duration amounted to 5.5 months for the general group and 5.4 for the triple-negative BC subgroup. As noted by the authors, eribulin therapy proved to be highly effective both for the general group (the objective response rate reached 54.4 %; the median PFS was 6.1 months, and the median OS – 10.6 months) and for the triple-negative BC subgroup (the objective response amounted to 55.1 %; the median PFS was 5.8 months, and the median OS – 9.8 months); 19.2 % of patients in the general group and 15.4 % of patients with a triple-negative subtype survived one year without progression. The indicators for 1-, 2-, and 3-year OS were 43.9 %, 23.9 %, and 13.8 % in the general group and 40.3 %, 17.6 %, and 9 % in the triple-negative mBC subgroup [19].

Japan has the most considerable experience in using eribulin; in 2020, the results of the largest national retrospective study NCT02371174 were presented; this study aimed to evaluate the efficacy and safety of eribulin chemotherapy in 637 patients who received treatment from 2014 to 2016 and were followed for at least 2 years [20]. The patients included in the study received eribulin treatment as the first- and second-line mBC chemotherapy in half of the cases (142 and 177 patients, respectively); in 317 patients, the drug was prescribed as the third and subsequent lines. Luminal HER2-negative cancer prevailed among the study patients (72.5 %); triple-negative cancer was diagnosed in 24.6 % of cases; bone (56.4 %), liver (48 %), and lung (40.2 %) metastases dominated among the metastasis sites. It is remarkable that only 56.5 % of patients who underwent eribulin therapy had the ECOG status 0; in every third case the ECOG status 1 was noted, and in 6 % of patients – ECOG 2; the study also included 5 patients (0.8 %) with the ECOG status 3. The average number of the introduced eribulin cycles amounted to 7.7 (from 1 to 36; the median – 5); the median of the relative dose intensity of eribulin was 0.74; 16 % of patients needed dose reduction. The median OS in the general group of patients was 15.6 months; 58.2 and 35.9 % of patients survived 1 and 2 years, respectively. In patients who received the drug as the first-line chemotherapy, those indicators were 22.8 months (median OS), 71.6 and 48.3 % (1- and 2-year OS), in the case of eribulin use in the second line – 16.3 months, 58.2 % and 37 %, respectively, and with the drug prescription in the third and subsequent lines – 12.6 months, 52 % and 29.5 %, respectively. A favorable safety profile of the treatment was noted by the authors; grade ≥3 adverse events were observed in 61.7 % of patients with dominating neutropenia (49.5 %) [20].

As can be seen from the above, the use of eribulin in the early-line mBC treatment makes it possible to obtain the highest treatment results; it is extremely important that the drug demonstrates efficacy in different metastasis sites and different biological BC subtypes, which contributes to its universality in various clinical settings.

Eribulin efficacy in visceral metastases

A particularly unfavorable predictive factor is expressed by the lesion of the visceral organs, especially with the onset of the mBC manifestation. Moreover, in the presence of liver lesion constitutinga significantly aggressive metastasis site, the death risk in BC patients doubles [21]. That is why the interest in evaluating the efficacy of various antitumor agents, including eribulin, in patients with visceral metastases is remarkably high.

In 2020, additional data derived from randomized studies 301 and 305 were presented, namely, an analysis of patients survival in the context of different metastasis sites [22]. The patients were divided into subgroups according to the localization of the tumor lesion (bones/liver/lymph nodes/lungs); a subgroup of soft tissue metastases was also identified; the group included patients with chest wall, skin, or breast lesions. 1.864 patients participated in the analysis (762 from study 301 and 1.102 from study 305); among them, 1.062 patients received chemotherapy with eribulin while the control group received capecitabine or the therapy chosen by the doctor. An advantage in OS in patients treated with eribulin compared with the control group – 14.9 vs 12.9 months, HR 0.86, was noted by the authors; the differences were significant in bone metastases – 14.6 vs 12.5 months, HR 0.76, lymph node metastases – 14.4 vs 11.8 months, HR 0.82, soft tissue lesions – 15.5 vs 11.2 months, HR 0.81 and, most importantly, in liver metastases – 13.4 vs 11.3 months, HR 0.84. It should be noted that the biological subtypes, when analyzed, showed that patients with luminal HER2-negative cancer had a statistically significant advantage of eribulin in increasing OS in patients with liver metastases (14.4 vs 12.5 months, HR 0.81) and bone lesions (14.7 vs 13.5 months, HR 0.79). At the same time, in hormone-negative BC, a significant prolongation of OS with eribulin therapy compared to the control group was observed in almost all subgroups, including bone metastases (13.8 vs 8.6 months, HR 0.62), lung metastases (11.3 vs 8.7 months, HR 0.77), lymph node metastases (11.6 vs 8.8 months, HR 0.69), and soft tissue lesions – 12.2 vs 8.7 months, HR 0.70. Noteworthy is that the percentage change in sum of target lesion diameters during the eribulin therapy was high both in visceral lesions (66 % – with liver metastases, 63 % – with lung metastases) and in non-visceral lesions (68 % – with lymph node lesions, 65 % – soft tissue metastases). Thus, the authors have proven the eribulin efficacy (both immediate and long-term) in various metastasis localizations, including liver and lung lesions [22].

In 2020, S. Kazmi et al. performeda separate analysis of the efficacy of different chemotherapy regimens for visceral metastases [23]. The analysis was based on the electronic database Cancer Treatment Centers of America (CTCA) and used data from 01/2012 to 10/2018 with the inclusion of 443 patients. All patients in the study had confirmed mBC with lung and/or liver lesions and received eribulin ($n = 229$), gemcitabine ($n = 134$), or capecitabine ($n = 80$) as the third-line treatment. It should be noted that the key characteristics of the patient groups treated with various cytostatics were similar. The patients' median age was 55 years; 69 % of patients had the ECOG status 0–1; hormone positive HER2-negative mBC was found in the majority of patients (62 %); 29 % were diagnosed with triple negative cancer. When comparing the patients' treatment results, the authors note that in the general group, the median OS was maximum in patients who received eribulin therapy in contrast to gemcitabine and capecitabine (9.8 vs 7.2 vs 9.1 months, respectively). In patients with triple negative cancer, eribulin is characterized by a trend in increased survival compared with gemcitabine (HR 0.82) and capecitabine (HR 0.77) while in patients with hormone positive HER2-negative mBC eribulin has an advantage

only over gemcitabine (HR 0.69), but not over capecitabine (HR 1.04). The authors analyzed the indicators of 1- and 2-year OS and obtained outstanding data: with eribulin therapy, those indicators were as high in the general group of patients (38 % and 7 %, respectively) as with a triple-negative subtype (35 % and 8 %, respectively) and hormone positive HER2-negative cancer (42 % and 7 %, respectively). With gemcitabine therapy, OS indicators in the general group were lower compared with eribulin treatment (30 % and 7 %, respectively), as well as in patients with triple negative cancer – 31 % and 3 %, and luminal BC – 27 % and 3 %, respectively. In those treated with capecitabine, the obtained indicators of 1- and 2-year OS were also inferior to eribulin: in the general group of patients – 30 % and 10 %, respectively, in triple negative cancer patients – 25 % and 15 %, respectively, and in the luminal HER2-negative cancer – 24 % and 7 %, respectively. Thus, monotherapy with eribulin as third-line treatment in routine practice appeared to be more effective than gemcitabine and capecitabine in visceral metastases whatever the biological subtype of the tumor [23].

Eribulin efficacy in brain metastases

The number of BC patients with brain lesion is progressively increasing year after year, which, on the one hand, is associated with improved diagnostic capabilities, and on the other hand, with an increase in the life expectancy of patients with advanced stage and their "living out" until the manifestation of cerebral metastases. Brain metastases are the most unfavorable BC metastasis site in terms of both the course and symptoms of the disease and prognosis, therefore, the search for effective cytostatics with a favorable safety profile becomes a highly urgent task [24].

Several retrospective studies addressed the eribulin efficacy in patients with brain metastases. Thus, in the study by A. Fabi et al., eribulin therapy was administered to 78 patients with mBC, and among them, 18 had brain metastases; the clinical efficacy of the drug in cerebral lesions reached 47 % and did not depend on the biological subtype of the tumor [25].

Similar data are presented in the work of Spanish colleagues; 20 out of 95 mBC patients treated with eribulin had brain metastases. A partial response and stabilized intracranial lesions were observed in 20 and 25 % of patients, respectively [26].

Special attention must be given to the results of the Italian population study EBRAIM in which the eribulin therapy efficacy was examined in 34 BC patients with brain lesions [27]; it is worth noting that in most cases (65 %), eribulin was used as the second- or third-line treatment. The patient cohort was young (with the median of 49 years); 91 % of patients had visceral metastases; luminal HER2-negative and triple-negative tumor subtypes were diagnosed in 58.8 and 29.4 % of cases, respectively. Less than half of the patients had single cerebral lesions; 47 % of patients had multiple brain lesions; leptomeningeal lesions were diagnosed in 5.8 %; radiation treatment to the brain area was used in 67.6 % of cases before starting the eribulin chemotherapy. The treatment results appeared to be remarkably productive: half of the patients demonstrated clinical efficacy; an objective response was noted in 26 % of cases, including a complete response in 9 % of patients; the disease stabilized in 23 % of patients. In regard to the response to eribulin therapy for intracranial lesions, it was also high: 14 % of patients had an objective response (including complete metastasis regression in 7 % of cases), and in 34 % the process stabilized. Clinical efficacy was persistent (for 3 and 6 months) in 41 and 21 % of patients, respectively, and in the patient with a leptomeningeal process, a partial response to eribulin therapy was observed for 9.2 months. The median before the appearance of new intracranial metastases was 5 months, and before extracranial progression – 4 months. A highly favorable safety profile of eribulin treatment was noted by the authors: 29 % of patients developed grade 3–4 neutropenia; other adverse events were reported in less than 10 % of cases [27].

Eribulin efficacy in elderly patients

Treatment of mBC in elderly patients seems to be a particularly non-trivial task for modern oncology; the prescribed cytostatic therapy requiresa special balance between the efficacy and safety of treatment. That is why the eribulin treatment results in patients representing the older age group are given special attention, both in the framework of randomized studies and while analyzing retrospective data.

A pooled analysis of data from three randomized studies (EMBRACE, study 201, and 211) evaluated the eribulin therapy efficacy in different age groups [28]; 827 patients received eribulin therapy, and among them, 253 patients were under 50, 289 patients were 50–59 years old, 206 were 60–69 years old, and 79 patients were ≥70 years old [9]. The analysis showed no differences in the eribulin therapy efficacy in those age groups: the median OS was 11.8 months, 12.3 months, 11.7 months, and 12.5 months, respectively, $p = 0.82$). In different age groups, similar results were obtained in regard to the median PFS (3.5 months, 2.9 months, 3.8 months, and 4.0 months, respectively, $p = 0.42$), level of objective response achievement (12.7 %, 12.5 %, 6.3 %, and 10.1 %, respectively), and clinical efficacy (20.2 %, 20.8 %, 20.4 %, and 21.5 %, respectively). It is important that the incidence of adverse events was also identical in different age groups. Thus, the efficacy and safety of eribulin therapy in patients ≥70 years old corresponds to that in other age groups, which makes it not only possible, but also advisable to use the drug in these clinical settings [28].

In 2017, the results of a large retrospective study REPROLINE were presented; the study examined 446 patients with mBC receiving eribulin chemotherapy in 12 cancer clinics in France between October 2014 and February 2017 [29]. The authors identified 2 patient groups: up to 70 years

old (n = 363) and over 70 years old (n = 83); the groups were comparable in terms of tumor characteristics, the number of tumor lesions, and previous chemotherapy lines (median – 2). In both groups, the patients received the same number of eribulin therapy cycles (median – 4) and exhibited identical efficacy results. Thus, the median PFS in elderly and younger patients was 3.7 vs 3.67 months, HR 0.972, the median OS – 10.7 vs 10.7 months, HR 0.997. Adverse events had a remarkably similar profile between the groups; grade 3–4 neutropenia was observed in 22.9 % (patients under 70 years old) vs 15.7 % (over 70 years old), fatigue – 6.5 vs 13.3 %, neurotoxicity – 4.4 vs 3.6 %; in 9.6 % of patients in each group, eribulin therapy was discontinued due to toxicity. With this in mind, the authors emphasize that the eribulin chemotherapy efficacy does not depend on the patients' age, and in patients of the older age group, the treatment is not only effective but also safe [29].

R. Luca et al. presented similar data in 2020 [30]; their observational study evaluated the efficacy and safety of eribulin therapy in patients over 70 years old with anthracycline- and taxane-resistant mBC; eribulin was administered ata dose of 1.23 mg/m^2 on days 1 and 8, every 3 weeks. 18 % of patients had a partial response to the therapy; the disease stabilized in 40 %; the median PFS and OS in the study were 3.2 and 12.8 months. A noteworthy peculiarity of the study appeared to be the dynamics evaluated for the level of blood marker CA 15-3 during the eribulin therapy; the authors suggested thata decrease in the CA 15-3 level of more than 50 % was associated with an increase in PFS. Moreover, eribulin therapy factored into a decrease in painful condition and an improvement in the quality of life in 47 % of patients according to the analysis of questionnaire EORTC QLQ-C30 [30].

In 2020, a pooled analysis of 5 studies was presented; it included 301 patients of the older age group (≥ 70 years old) who received eribulin treatment for mBC [31]. An objective response to eribulin therapy was achieved in 23.2 % of patients; the disease was controlled in 47 %; the median PFS and OS were 4.8 and 13.1 months, respectively. The treatment demonstrated a quite favorable safety profile with the low frequency of grade 3–4 adverse events: neutropenia was registered in 0–49 %, fatigue – 5.0–16.5 %, and neurotoxicity – 0–10.1 %. Eribulin dose reduction was required in 40 % of cases. As summarized by the authors, the eribulin chemotherapy efficacy and safety profile in elderly patients corresponds to the general population; the drug demonstrates a satisfactory balance between efficacy and safety in pretreated mBC [31].

Russian experience of using eribulin in routine practice

Owing to the accumulated experience of eribulin use in routine practice of oncologists in Russia, it was possible to conduct a large population analysis of the efficacy and safety of the drug therapy in 459 Russian women from 44 federal and municipal medical institutions of our country from 2014 to 2018 [32]. All patients had mBC and received eribulin therapy in accordance with the indications for the drug use registered in the Russian Federation (the second and subsequent lines of chemotherapy for mBC pretreated with anthracyclines and taxanes) in the standard regimen – 1.4 mg/m^2 intravenously on days 1 and 8 of a 21-day cycle. In the Russian study, 83 % of patients had HER2-negative cancer (49.9 % – a luminal subtype and 33.1 % – triple negative cancer); visceral lesions were diagnosed in the majority of patients (73 %), moreover, a metastatic lesion of 3 areas or more was noted in 41.6 % of cases. The previous chemotherapy with anthracyclines and taxanes was used in 94 % of patients; in 38 % of cases, patients also received capecitabine; the median of the previous treatment lines for mBC was 2. An objective response to eribulin therapy was noted by the authors in 20.5 % of cases (a full response – 3.2 %, and a partial one – 17.3 %); the disease stabilized in 52.7 % of women, moreover, in 20 % of cases, the duration exceeded 6 months. The objective response rate in the group of luminal tumors was higher compared to triple negative cancer: 23.5 % vs 15.8 %; the tumor growth was controlled in 76.9 % vs 67.8 %, respectively; p <0.05. The median PFS amounted to 4.83 months (5.17 months for luminal cancer and 4.0 months for the triple-negative subtype). It should be noted that the maximum drug efficacy was observed when used in the early-line treatment (≤ the third line): the objective response rate and tumor growth control reached 24.2 and 82.2 %, respectively, and the median PFS amounted to 5.07 months; when eribulin was used in the fourth and subsequent lines, the objective response rate was 15.4 %, tumor growth control – 58.6 %, and the median PFS amounted to 4.27 months, p <0.05. In addition, 19 % of cases were marked by "special sensitivity" to eribulin: 48.6 % of patients exhibited an objective response; long-term stabilization fora period of 8 months or more was registered in 51.4 %; moreover, that phenomenon did not depend on the biological subtype of the tumor or metastasis localization. The eribulin therapy demonstrated a favorable safety profile; dose reduction by 1 level was required in only 14 % of cases [32].

Thanks to a large sample of Russian women who received eribulin treatment as part of routine clinical practice, important analyses of efficacy and safety took place to examine various clinical settings, including elderly patients and patients with brain metastases. In the Russian pooled analysis, there wasa particularly significant group of patients over 60 years old (133 cases, 24.6 %); the efficacy of eribulin in elderly patients was identical to that in patients under 60. Thus, the objective response rate was 18.8 % vs 21.3 %, the median PFS amounted to 4.27 vs 5.1 months, p = 0.156. The therapy showed a favorable safety profile independent of the women's age [32].

Of particular interest was the analysis of a patient subgroup (n = 35) with metastatic brain lesions [33]; the women's median age amounted to 52 years; in most cases (68.6 %)

the patients had 2 or more areas of metastatic lesion; radiation therapy to the brain area (remote or stereotaxic) was used in 62.8 % of cases before starting the eribulin treatment, and in 5.8 % – during the eribulin chemotherapy. The clinical efficacy of eribulin therapy in patients with brain metastases reached 48.6 %, including a partial response in 20 % of patients; the disease stabilized in 62.9 %; the tumor growth was controlled in 82.9 % of cases. It is highly important that the eribulin therapy efficacy did not depend on the applied radiation therapy to the brain area; the median PFS in the general group was 4.1 months, in patients after radiation therapy – 4.1 months, without radiation therapy – 3.47 months, $p = 0.798$. Thus, the eribulin use for brain metastases is absolutely justified; the drug has demonstrated its efficacy in a retrospective analysis based on the Russian patient population [33].

The second pooled Russian analysis addressing the use of eribulin in routine practice was presented in 2021 and concerned only patients with hormone positive HER2-negative mBC with a history of a prior therapy with CDK4/6 inhibitors [34]. 54 patients receiving eribulin treatment in 24 oncological institutions in our country over the past years were included in the analysis. All patients had luminal HER2-negative mBC, for which they received combined endocrine therapy with CDK4/6 inhibitors (palbociclib or ribociclib); the therapy was followed by the disease progression (in the first 6 months – in 51.9 %, and in the period from 6 to 38 months – in 48.1 % of cases). The patients' median age was 56 years; 75.9 % of patients had recurrent cancer, 24.1 % – primary disseminated BC; in 94.4 % of cases, chemotherapy with anthracyclines and taxanes preceded eribulin; 89.1 % had visceral metastases at the time of initiating the eribulin therapy (liver metastases – 65.5 %, lung metastases – 52.8 %); tumor lesions of the brain had 7.5 % of patients. It should be noted that in the majority of patients (90.7 %), eribulin was used in the initial lines of therapy for hormone positive HER2-negative mBC: in the 2nd line – in 61.1 %, in the 3rd line – in 29.6 %, and eribulin was prescribed extremely rarely – only in 7.4 and 1.9 % of patients, respectively – in the late lines (4th and 5th). The number of eribulin chemotherapy courses ranged from 1 to 44 with the median of 8 and the mean of 10.5. With a median follow-up of 11.5 months (from 3 to 36 months), the authors obtained the following results: a partial response was noted in 24.4 %, stabilization – in 66.7 % of cases, and progression – in 8.9 % of patients. The median PFS for the eribulin therapy was 10.0 months; 6-month, 1-year, and 2-year PFS amounted to 79.5, 44.8, and 26.5 %, respectively. With a median follow-up of 11.5 months, 92.6 % of patients remain alive, and 55.6 % continue chemotherapy with eribulin. It is extremely important that the drug appeared to be effective regardless of the patients' age, previous treatment, presence of visceral metastases, and liver involvement. The safety profile was favorable; adverse events were noted in 34.5 % of patients, which required dose adjustment in 18.5 % of cases [34]. The results of the presented pooled observational Russian study coincide with the data obtained from the large American observational study EMPOWER where 395 patients with hormone positive HER2-negative mBC received eribulin after progression during treatment with CDK4/6 inhibitors [35]. In the group of patients who received chemotherapy with eribulin in accordance with the indications registered in the USA (third line of chemotherapy for advanced stage, after anthracyclines and taxanes), there were 135 patients who had visceral metastases in 92.6 % of cases. Pursuant to the authors, eribulin proved to be highly effective in those difficult clinical settings: an objective response was noted in 26.7 %, clinical efficacy – in 54.1 % of cases; the median PFS was not achieved, and 6-month PFS amounted to 70.4 % [34, 35].

Conclusion

Thus, the results of the pooled Russian analyses demonstrate the eribulin efficacy in a variety of clinical settings: in patients with pretreated BC, with visceral metastases and brain lesion, in different age groups (including elderly patients), as well as in patients with a hormone-resistant variant of the disease after progression following treatment with CDK4/6 inhibitors. These data are remarkably similar not only to the results of previously conducted registration randomized studies but also to the results derived from population analyses. The geography of retrospective studies evaluating the eribulin chemotherapy efficacy in routine practice is particularly wide, which once again confirms the continuing high interest in the drug expressed by oncologists around the world.

ЛИТЕРАТУРА/REFERENCES

1. Cancer Today. Available at: https://gco.iarc.fr/today/online-analysis.
2. Instructions for the medical use of the drug Halaven (RU LP-001782 of 28.07.2012, with changes of 29.11.2018). (In Russ.).
3. Cardoso F., Paluch-Shimon S., Senkus E. et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31(12):1623–49. DOI: 10.1016/j.annonc.2020.09.010.
4. Zhukova L.G., Andreeva Yu.Yu., Zavalishina L.E. et al. Breast cancer. Sovremennaya onkologiya = Modern Oncology 2021;23(1):5–40. (In Russ.). DOI: 10.26442/18151434.2021.1.200823.
5. Cortes J., O'Shaughnessy J., Loesch D. et al. Eribulin monotherapy *versus* treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011;377:914–23. DOI: 10.1016/S0140-6736(11)60070-6.
6. Kaufman P.A., Awada A., Twelves C. et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated

with an anthracycline and a taxane. J Clin Oncol 2015;33(6):594–601.
7. Pivot X., Im S., Guo M. et al. Subgroup analysis of patients with HER2-negative metastatic breast cancer in the second-line setting from a phase 3, open-label, randomized study of eribulin mesilate versus capecitabine. Breast Cancer 2018;25(3):370–4. DOI: 10.1007/s12282-017-0826-4.
8. Cortes J., Schoffski P., Littlefield B. Multiple modes of action of eribulin mesylate: Emerging data and clinical implication. Cancer Treat Rev 2018;70:190–8.
9. Funahashi Y., Okamoto K., Adachi Y. et al. Eribulin mesylate reduces tumor microenvironment abnormality by vascular remodeling in preclinical human breast cancer models. Cancer Sci 2014;105(10):1334–42.
10. Ozawa Y., Okamoto K., Adachi M. et al. Supression of metastasis and improvement of drug distribution by eribulin mesylate. Presented at: EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, November 18–21, 2014, Spain, Barcelona.
11. Yoshida T., Ozawa Y., Kimura T. et al. Eribulin mesilate suppresses experimental metastasis of breast cancer cells by reversing phenotype from epithelial-mesenchymal transition (EMT) to mesenchymal-epithelial transition (MET) states. Br J Cancer 2014;110:1497–505.
12. Dezs Z., Oestreicher J., Weaver A. et al. Gene expression profiling reveals epithelial mesenchymal transition (EMT) genes can selectively differentiate eribulin sensitive breast cancer cells. PLoS One 2014;9:e106131.
13. Takaaki F., Shoko T., Yuko N. et al. Eribulin suppresses new metastases in patients with metastatic breast cancer. In Vivo 2020;34:917–21. DOI: 10.21873/invivo.11858.
14. Garrone O., Montemurro F., Saggia Ch. et al. Eribulin in pretreated metastatic breast cancer patients: results of the TROTTER trial – a multicenter retrospective study of eribulin in real life. SpringerPlus 2016;5:59. DOI: 10.1186/s40064-016-1700-0.
15. Barni S., Fontanella C., Livraghi L. et al. A broad Italian experience with eribulin mesylate in metastatic breast cancer patients: the ESEMPiO study. Abstract e11539. DOI: 10.1200/jco.2015.33.15_suppl.e11539.
16. Zhao Y., Xie N., Li W. et al. Real-world effectiveness of eribulin in heavily pretreated patients with metastatic breast cancer in China: a multicenter retrospective study. Ther Adv Med Oncol 2021;13:1–13. DOI: 10.1177/17588359211030210.
17. Adamo V., Ricciardi G., Giuffrida D. et al. Eribulin mesylate use as third-line therapy in patients with metastatic breast cancer (VESPRY): a prospective, multicentre, observational study. Ther Adv Med Oncol 2019;11:1–7. DOI: 10.1177/1758835919895755.
18. Krasniqi E., Pizzuti L., Valerio M. et al. Second-line eribulin in triple negative metastatic breast cancer patients. Multicentre retrospective study: The TETRIS Trial. Int J Med Sci 2021;18(10):2245–50. DOI: 10.7150/ijms.54996.
19. Mougalian S., Kish J., Zhang J. et al. Effectiveness of eribulin in metastatic breast cancer: 10 years of real-world clinical experience in the United States. Adv Ther 2021;38:2213–25. DOI: 10.1007/s12325-020-01613-6.
20. Inoue K., Takahashi M., Mukai H. et al. Effectiveness and safety of eribulin in Japanese patients with HER2-negative, advanced breast cancer: a 2-year post-marketing observational study in a real-world setting. Invest New Drugs 2020;38(5):1540–9. DOI: 10.1007/s10637-019-00890-546.
21. Haeyoung K., Doo Ho Ch., Won P. et al. Prognostic factors for survivals from first relapse in breast cancer patients: analysis of deceased patients. Radiat Oncol J 2013;31(4):222–7. DOI: 10.3857/roj.2013.31.4.222.
22. O'Shaughnessy J., Cortes J., Twelves C. et al. Efficacy of eribulin for metastatic breast cancer based on localization of specific secondary metastases: a post hoc analysis. Sci Rep 2020;10:11203. DOI: 10.1038/s41598-020-66980-0.
23. Kazmi S., Chatterjee D., Raju D. et al. Overall survival analysis in patients with metastatic breast cancer and liver or lung metastases treated with eribulin, gemcitabine, or capecitabine. Breast Cancer Res Treat 2020;184:559–65. DOI: 10.1007/s10549-020-05867-0.
24. Saunus J.M., McCart Reed A.E., Leong Lim Zh., Lakhani S.R. Breast cancer brain metastases: clonal evolution in clinical context. Int J Mol Sci 2017;18(1):152. DOI: 10.3390/ijms18010152.
25. Fabi A., Moscetti L., Ciccarese M. et al. Eribulin in heavily pretreated metastatic breast cancer patients and clinical/biological feature correlations: impact on the practice. Future Oncol 2015;11(3):431–8. DOI: 10.2217/fon.14.271.
26. Sirvén M., Fernández-Ortega A., Stradella A. at al. Real-world efficacy and safety of eribulin in advanced and pretreated HER2-negative breast cancer in a Spanish comprehensive cancer center. BMC Pharmacol Toxicol 2019;20(1):68. DOI: 10.1186/s40360-019-0367-x.
27. Fabi A., Terrenato I., Vidiri A. et al. Eribulin in brain metastases of breast cancer: outcomes of the EBRAIM prospective observational trial. Future Oncol 2021;17(26):3445–56. DOI: 10.2217/fon-2021-0300.
28. Muss H., Cortes J., Vahdat L. et al. Eribulin monotherapy in patients aged 70 years and older with metastatic breast cancer. Oncologist 2014;19(4):318–27. DOI: 10.1634/theoncologist.2013-0282.
29. Martin-Babau J., Robert M., Seegers V. et al. Eribulin is safe and efficient in metastatic breast cancer in elderly patients. Results from the REPROLINE multicentric retro-prospective cohort. Available at: https://www.annalsofoncology.org/article/S0923-7534(20)37723-1/pdf.
30. Luca R., Alu M., Genova G. et al. Use of eribulin mesylate as second-line therapy in elderly patients with HER2 negative metastatic breast cancer (MBC): efficacy, tolerability and quality of life. Eur Rev Med Pharm Sci 2020;24:12727–34.
31. Pedersini R., Mauro P., Amoroso V. et al. Efficacy of eribulin mesylate in older patients with breast cancer: a pooled analysis of clinical trial and real-world data. J Geriatr Oncol 2020;11(6):976–81. DOI: 10.1016/j.jgo.2020.03.021.
32. Gorbunova V.A., Kolyadina I.V., Kovalenko E.I. et al. Efficacy and safety of eribulin in HER2-negative metastatic breast cancer: data from many years of experience from real clinical practice in Russia. Sovremennaya onkologiya = Modern Oncology 2019;21(1):12–23. (In Russ.). DOI: 10.26442/18151434.2019.1.190250.
33. Kolyadina I.V., Bulavina I.S., Petkau V.V. et al. Potential of using eribulin in metastatic brain lesions in breast cancer patients: scientific background and Russian clinical experience. Sovremennaya onkologiya = Modern Oncology 2019;21(2):17–24. (In Russ.). DOI: 10.26442/18151434.2019.2.190395.
34. Kolyadina I.V., Abidova N.R., Akopyan A.A. Analysis of the efficacy and safety of eribulin therapy in patients with HR+ HER2-negative metastatic breast cancer, pretreated with CDK4/6 inhibitors in real Russian practice. Sovremennaya onkologiya = Modern Oncology 2021;23(1):68–76. (In Russ.). DOI: 10.26442/18151434.2021.1.200769.
35. Mougalian S.S., Feinberg B.A., Wang E. et al. Observational study of clinical outcomes of eribulin mesylate in metastatic breast cancer after cyclin-dependent kinase 4/6 inhibitor therapy. Future Oncol 2019;15(34):3935–44. DOI: 10.2217/fon-2019-0537.

ORCID of author
I.V. Kolyadina: https://orcid.org/0000-0002-1124-6802

Conflict of interest. The author declares no conflict of interest.

Financing. The work was performed without external funding.

Article submitted: 03.08.2021. **Accepted for publication:** 04.10.2021.