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A rational approach to dose reduction of CDK4/6 inhibitors in the treatment of patients with advanced breast cancer: a Narrative Review

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The use of CDK4/6 inhibitors in the treatment of $HR^+/HER2^-$ breast cancer (BC) has become increasingly widespread in recent years. When assessing the safety of CDK4/6 inhibitors, it was found that during therapy, a significant number of patients require a reduction in the initial dose of the drug due to adverse events (dose reduction), but publications summarizing such data are absent. At the same time, the time to dose reduction and its stages can significantly affect the organization of drug supply for patients with drugs of this group, having an economic and administrative effect on the healthcare system. In this regard, a review of the results of the use of CDK4/6 inhibitors presented in the literature, describing the features of dose reduction, is timely and relevant.

The aim. To conduct a literature review in order to summarize and systematize the results of the use of CDK4/6 inhibitors, describing the features of dose reduction.

Materials and methods. The literature search was carried out in the MedLine (PubMed) and Google Scholar databases from January 2016 to January 2024. The literature search was carried out using the following search queries: "ribociclib OR palbociclib OR abemaciclib" AND "breast cancer and randomized clinical trial", "CDK4/6 inhibitors OR cyclin-dependent kinase 4/6 inhibitors" AND "metastatic breast cancer" AND "real-world" AND "dose Intensity OR dose reduction". As a result of the search, 384 publications were found, and 15 publications were included in the final analysis. Data on dose reduction were systematized according to the following criteria: the proportion of patients who underwent the first and, if available, the second reduction, the time to dose reduction, and the intensity of dosing.

Results. Analysis of data from randomized clinical trials showed that a dose reduction was required in 31.8–57.4% of patients using CDK4/6 inhibitors. At the same time, the second dose reduction was carried out in 17.4–40% of patients. The median time to the first stage of reduction ranged from 1.2 to 3.2 months. The median relative dose intensity ranged from 66.3 to 93.0%. According to the results of the analysis of real clinical practice data, dose reduction was carried out in 28.1–59.1% of patients. At the same time, the first stage of reduction was carried out at 1–3 months of therapy, and the second at 4–17 months from the start of treatment.

Conclusion. A literature review was conducted to systematize the results of the use of CDK4/6 inhibitors, describing the features of dose reduction. Approximately up to 60% of patients need a dose reduction, regardless of the selected CDK4/6 inhibitor. Data on the frequency and time to dose reduction vary; therefore, the need for reduction in an individual patient may arise at any time, which may complicate the process of planning the provision of anti-tumor therapy drugs.

Keywords: $HR^+/HER2^-$; breast cancer; CDK4/6 inhibitor; abemaciclib; palbociclib; ribociclib; dose reduction

Abbreviations: BC — breast cancer; HR — hormone receptor; HER2 — human epidermal growth factor receptor 2; EGFR — epidermal growth factor receptor; RCT — randomized clinical trial; CDK — D-cyclin-dependent kinase; Rb — retinoblastoma.

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Рациональный подход к редукции дозы ингибиторов CDK4/6 при лечении пациентов с распространённым раком молочной железы: описательный обзор

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Применение ингибиторов CDK4/6 при лечении $HR^+/HER2^-$ рака молочной железы (РМЖ) в последние годы получает все большее распространение. При оценке безопасности ингибиторов CDK4/6 было установлено, что в процессе терапии значительному числу пациентов требуется снижение первоначальной дозы препарата в связи с нежелательными явлениями (редукция дозы). Однако публикации, обобщающие такие данные отсутствуют. При этом время до редукции дозы, ее этапность, могут значительно влиять на процесс организации лекарственного обеспечения пациентов препаратами этой группы, оказывая экономический и административный эффект на систему здравоохранения. В связи с этим, проведение обзора представленных в литературе результатов применения ингибиторов CDK4/6, описывающих особенности снижения дозы, своевременно и актуально.

Цель. Провести обзор литературы с целью обобщения и систематизации результатов применения ингибиторов CDK4/6, описывающих особенности редукции дозы.

Материалы и методы. Поиск литературы проводился в базах данных MedLine (PubMed) и Google Scholar с января 2016 по январь 2024 года. Литературный поиск был проведён по следующим поисковым запросам: «ribociclib OR palbociclib OR abemaciclib» AND «breast cancer and randomized clinical trial», «CDK4/6 inhibitors OR cyclin-dependent kinase 4/6 inhibitors» AND «metastatic breast cancer» AND «real-world» AND «dose Intensity OR dose reduction». В результате поиска было найдено 384 публикации, в финальный анализ попали 15 публикаций. Систематизацию данных о редукции доз проводили по следующим критериям: доля пациентов, которым выполнена первая и, при наличии, вторая редукция, время до редукции дозы, интенсивность дозирования.

Результаты. Анализ данных рандомизированных клинических исследований показал, что снижение дозы потребовалось 31,8–57,4% пациентам при применении ингибиторов CDK4/6. При этом 17,4–40% пациентам было проведено второе снижение дозы. Медианное время до первого этапа редукции составило от 1,2 до 3,2 мес. Медиана относительной эффективности дозы находилась в интервале от 66,3 до 93,0%. По результатам анализа данных реальной клинической практики — 28,1–59,1% пациентам была проведена редукция дозы. При этом первый этап редукции осуществлялся на 1–3 мес. терапии, а второй — на 4–17 мес. с момента начала лечения.

Заключение. Проведён обзор литературы для систематизации результатов применения ингибиторов CDK4/6, описывающих особенности редукции дозы. Примерно до 60% пациентов нуждаются в проведении редукции дозы вне зависимости от выбранного ингибитора CDK4/6. Данные о частоте и времени до снижения дозы разнятся, следовательно, необходимость редукции у отдельного пациента может возникнуть в любой момент, что может затруднять процесс планирования обеспечения препаратами противоопухолевой терапии.

Ключевые слова: $HR^+/HER2^-$; рак молочной железы; ингибитор CDK4/6; абемациклиб; палбоциклиб; рибоциклиб; редукция дозы

Список сокращений: РМЖ — рак молочной железы; HR — рецептор гормона; HER2 — рецептор эпидермального фактора роста, тип 2; EGFR — рецептор эпидермального фактора роста; РКИ — рандомизированное клиническое исследование; CDK — D-циклин-зависимая киназа; Rb — ретинобластома.

INTRODUCTION

Most cases (approximately 70%) of breast cancer (BC) worldwide are positive for hormonal receptor and/or progesterone receptor (HR) expression and do not express human epidermal growth factor receptor 2 (HER2), i.e., have the $HR^+/HER2^-$ phenotype[1] [1]. Although blocking signaling from epidermal growth factor receptors (EGFR) is a base of $HR^+/HER2^-$ BC treatment, many patients develop resistance to endocrine therapy. This resistance is difficult to overcome and is associated with a negative prognosis [2–4]. A number of mechanisms are involved in the development of resistance to endocrine therapy, including changes in cell cycle checkpoints. For example, regulation of cyclin

[1] National Cancer Institute. SEER. Cancer Stat Facts: Female Breast Cancer Subtypes. Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html.

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D-cyclin-dependent kinase (CDK) 4/6 with INK4 proteins and the retinoblastoma (Rb) pathway (CDK4/6-INK4-Rb), which affects cell proliferation, is often impaired in HR^+ BC and other types of cancer [5–7]. Constant expression of cyclin D1 and phosphorylation of Rb support the use of CDK4/6 inhibitors in HR^+ BC [8]. Inhibition of the CDK4/6-INK4-Rb pathway along with endocrine therapy may be effective in patients with $HR^+/HER2^-$ BC compared with endocrine therapy alone. Currently, three selective CDK4/6 inhibitors are registered in the Russian Federation: ribociclib, palbociclib, and abemaciclib [9]. Differences between these drugs include, above all, dosing regimens (ribociclib and palbociclib are used once daily for 3 weeks with a 1-week break, abemaciclib twice daily) and different selectivity for CDK4 compared to CDK6, which has been shown in some preclinical studies [10–13].

When assessing the safety of CDK4/6 inhibitors, it was found that during therapy, a significant number of patients require a reduction in the initial dose of the drug (reduction, dose modification) due to the occurrence of various adverse events [14, 15]. Unlike reducing the frequency of the required dose, reduction allows managing drug toxicity while maintaining the effectiveness of therapy and adherence to treatment [14, 16]. At the same time, the time to dose reduction and its stages can significantly affect the organization of drug supply for patients with drugs of this class, having an economic and administrative impact on the healthcare system. In this regard, an actual question is the analysis of the data available in the literature on the features of dose reduction when using drugs of this group.

THE AIM. To conduct a literature review to systematize the results of the use of CDK4/6 inhibitors, describing the features of dose reduction of drugs.

MATERIALS AND METHODS

A literature search was conducted in the MedLine (PubMed) and Google Scholar databases from 2016 to January 2024. The literature search was carried out using the following search queries:

For **PubMed**, the following filters were used: “since 2016”, “English language”, “preprints excluded”.

- (ribociclib OR palbociclib OR abemaciclib) AND breast cancer AND randomized clinical trial;
- (CDK4/6 inhibitors OR cyclin-dependent kinase 4/6 inhibitors) AND (metastatic breast cancer) AND real-world AND (dose Intensity OR dose reduction);

For **Google Scholar**, the filter “from 2016” was used.

- (CDK4/6 inhibitors OR cyclin-dependent kinase 4/6 inhibitors, metastatic breast cancer, real-world data, (dose intensity OR dose reduction).

A search for real-world clinical practice studies was additionally carried out in the Google Scholar system due to the frequent lack of their indexing in PubMed.

The literature search and preparation of the review were carried out in accordance with the PRISMA methodology[2].

It is worth noting that randomized clinical trials (RCTs) are currently the “gold standard” for assessing the clinical efficacy and safety of drugs [17, 18]. Despite the limitations due to the design of RCTs, such as strict inclusion and exclusion criteria for patients in the study population, the inability to assess the long-term consequences of the therapy under study, and systematic errors, the homogeneity of the data obtained in them is significantly higher than that of real-world clinical practice data (electronic medical records, registers, prescription data and reports of adverse events, data obtained from patients, data from mobile applications and wearable devices, etc.). In this regard, preference was given to RCTs in the selection of publications. However, RCTs that allow simultaneous comparison of all three CDK4/6 inhibitors in terms of frequency, duration, and proportion of patients requiring dose reduction are not available. Therefore, real-world clinical practice data cannot be neglected, because, of course, they should be taken into account as a supplement to RCTs [19].

Article and data selection was carried out independently by two researchers. Disagreements were resolved through discussion. Studies that met the following criteria were excluded:

- Therapy for another nosology against the background of CDK4/6 inhibitors;
- Line of therapy after discontinuation of CDK4/6 inhibitors;
- Use of CDK4/6 inhibitors as part of neoadjuvant therapy;
- Use of CDK4/6 inhibitors in combination with immunobiological drugs;
- Works that do not contain quantitative information about dose reduction (intensity, time to reduction, proportion).

Inclusion criteria were:

- Clinical trials and real-world clinical practice studies evaluating the use of CDK4/6 inhibitors in the treatment of patients with metastatic $HR^+/HER2^-$ advanced breast cancer;
- Clinical trials and real-world clinical practice studies evaluating dose reduction or dose intensity of CDK4/6 inhibitors used;

[2] The PRISMA2020 statement: An updated guideline for reporting systematic reviews. Available from: https://www.equator-network.org/reporting-guidelines/prisma/

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- Real-world clinical practice studies including all three CDK4/6 inhibitors (ribociclib, palbociclib, and abemaciclib).

Suitable data extraction, met the inclusion criteria, was carried out independently by two authors. The following information was extracted: name, surname and initials of the first author, year of publication, journal, type of study, patient condition, age and number of patients, treatment regimen, response to therapy, study design, as well as data on dose reduction (proportion of patients who underwent the first and, if available, second reduction, time to dose reduction, dosing intensity). The data obtained were combined without quantitative synthesis of the results of individual homogeneous studies using meta-analysis) [22].

Quantitative data on dose reductions were extracted together with confidence intervals (CI), minimum and maximum data values where this information is presented, however, CIs were not applicable to the proportions of patients who underwent reduction because the proportion of patients is not an average value.

Figure 1 shows a diagram reflecting the publication search strategy.

Publications systematizing data on dose reduction for all three CDK4/6 inhibitors were not found. In this regard, a summary of the data currently available in the literature on this issue is presented below, and potential problems related to adherence to therapy are also discussed.

RESULTS

Data on dose modification presented in RCTs are summarized in Table 1.

In extensive large-scale studies PALOMA-2 and PALOMA-3, the dose reduction of palbociclib is initially carried out from 125 to 100 mg, at the second stage — from 100 mg to 75 mg. In postmenopausal patients, according to PALOMA-2, the median relative dose intensity was 93% in the palbociclib group, and a reduction was required for 39.4% of patients. At the same time, the median time to the first dose reduction was 3.2 months. (1–28 months). A second reduction was necessary for 36% of patients [13, 20, 21]. A detailed analysis of the PALOMA-3 study [21, 23] showed that the median relative dose intensity was comparable to the data in PALOMA-2 and amounted to 89.8%, for placebo — 100%. In the palbociclib group, 42.3% in pre- and 31.8% of postmenopausal patients required a dose reduction. Among patients who had only one dose reduction, the median time to reduction was 57.0 days (from 125 to 100 mg) and 36.0 days (from 125 to 75 mg). In patients who underwent two dose reductions, the average time to the first reduction was 33.5 days (from 125 to 100 mg), and the average time to the second was 119.5 days (from 100 to 75 mg). Among patients in the palbociclib group who had at least one dose reduction, only 31% received treatment at a dose of 100 mg and 9% — 75 mg [22]. Thus, according to the results of clinical studies of palbociclib, dose reduction was required in an average of 39.4–42.3% of patients. According to the combined analysis of J. Ettl et al. [21], which included the results of palbociclib studies PALOMA-1, -2, -3, 413 patients out of 875 (47.2%) required a dose reduction. At the same time, a second dose reduction was required for 105 out of 413 patients (24.4%). The median time to the first dose reduction in the combined analysis was 70 days (interval 15.0–1269.0 days). The median time to the second dose reduction was 106.0 days (interval 29.0–699.0 days). [21] The wide range of time to reduction may indicate that the occurrence of such a need depends on the individual characteristics of patients and cannot be predicted in advance.

Abemaciclib dose reduction is described in the MONARCH-2 and MONARCH-3 studies and was required in 42.9 and 43.6% of patients, respectively. The first reduction was carried out from 150 to 100 mg, and the second from 100 to 50 mg [24, 25]. The median relative dose intensity was 86% for abemaciclib and 98% for the placebo group [25]. With a median follow-up of 17.8 months, the median number of cycles of therapy received in the abemaciclib group was 16, in the placebo group — 15 cycles [25]. Data on the time to the onset of the first and second dose modification, as well as the distribution of patients between them — were absent. According to the combined analysis of M.P. Goetz et al. [26], which includes the results of abemaciclib studies MONARCH 2 and -3, 42.7% of patients (under 65 years of age), 55.4% of patients (from 65 to 75 years of age) and 55.4% of patients (over 75 years of age) required dose reductions.

The MONALEESA-2, MONALEESA-3, and MONALEESA-7 studies describe data on dose reduction with ribociclib in a total of 1153 patients. The first reduction was from 600 to 400 mg/day, and the second was from 400 to 200 mg/day. Dose reduction was independent of age and ECOG (Eastern Cooperative Oncology Group) performance status. The exception is patients in the Asian population, among whom the proportion of patients who required a dose reduction was higher than that of patients without dose reduction in the MONALEESA-3 and -7 studies

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(MONALEESA-3 — 16.3 and 7.5%; MONALEESA-7 — 40.7 and 28.4%, respectively). In the MONALEESA-2 study, the median relative dose intensity for the ribociclib group was 65.6%, and for the placebo group — 99.3% [14]. Dose reduction was required in 57.4% of patients in the ribociclib group. Moreover, a second dose reduction was required in 40% of patients. The median time to the first dose reduction was 3 months [14]. In the MONALEESA-3 study, the median relative dose intensity for the ribociclib group was 67.8%, and for the placebo group — 99.7% [14]. Dose reduction was required in 38.7% of patients in the ribociclib group. Moreover, a second dose reduction was required in 17.4% of patients. The median time to the first dose reduction was 2.8 months [14]. In the MONALEESA-7 study, dose reduction was required in 37% of patients in the ribociclib group. Moreover, a second dose reduction was required in 27.5% of patients. The median time to the first dose reduction was 2.2 months [14]. Thus, according to the results of clinical studies of ribociclib, dose reduction was required in 38.7–57.4% of patients, which averages 45.8% [14]. Among patients who required a dose reduction of ribociclib, the majority are those patients who required a single reduction (257 out of 375 — 68.5%). The average time to the first dose reduction of ribociclib from the start of the study ranged from 2 to 3 months and generally corresponded in all three studies (MONALEESA-2 — 3.0 months, MONALEESA-3 — 2.8 months, MONALEESA-7 — 2.2 months).

The above data from RCTs and pooled analyses are confirmed by the results of routine practice studies. It should be noted that a significant number of patients receiving CDK4/6 inhibitors required a dose reduction due to toxicity (38.7–57.4%). The results of the dose reduction analysis in real-world clinical practice studies are reflected in Table 2. RCTs are certainly the “gold standard” in terms of the homogeneity of the data obtained, but the above-mentioned studies did not conduct a direct comparison between different drugs in this class. In addition, more detailed data related to dose reduction were not published. Thus, the analysis of real-world clinical practice studies included only those studies in which data for all three drugs in this class — abemaciclib, palbociclib, ribociclib — were simultaneously present, as well as studies in which information on the time to the second dose reduction was provided.

Summarizing the results of real-world clinical practice studies, dose reduction was required in 28.1–57.1% of patients receiving CDK4/6 inhibitors. The time to the first dose reduction ranged from 1 to 3 months, and the time to the second reduction ranged from 4 to 17 months from the start of therapy. The mean relative dose intensity (where it was taken into account) ranged from 0.8 to 0.83.

DISCUSSION

Thus, the need for dose reduction is an urgent fact in a significant proportion of patients (28.1–57.4%) receiving drugs of this class, regardless of menopausal status [14, 30]. Despite the fact that the drug class is well studied, detailed data on dose reduction are rarely found in publications. The few data on the time to dose reduction in RCTs and real-world clinical practice studies have a wide range of values (from 1 month to several years) [14, 30].). At the same time, it is impossible to predict when and in what volume a dose reduction will be required for a particular patient. When starting therapy for patients with drugs in this group, you need to be prepared for the need to reduce the dose at any stage of therapy. A complex dose reduction system can create additional problems when correcting therapy for $HR^+/HER2^-$ breast cancer with CDK4/6 inhibitors. It should be noted that only ribociclib has a dose reduction step of 200 mg, which corresponds to the dosage of the drug, i.e., allows it to be carried out by reducing the dose by one dose [14] (Fig. 2).

For the other two drugs — abemaciclib and palbociclib — dose reduction requires prescribing the drug in a different dosage, which may lead to a decrease in adherence to therapy and depends on the availability of specific drug dosages in the drug supply system [33]. Moreover, the pharmacokinetic parameters of the drugs may further limit the selection of dosages: the absorption process of abemaciclib is obviously saturable, as a result of which a reduction in the daily dose due to taking large doses once a day, instead of twice a day of a reduced dose, may lead to a violation of the therapeutic concentration of the drug in the blood. The conclusion about the undesirability of prescribing abemaciclib once a day is confirmed by the results of mathematical modeling [34]. The relevance of these issues is due to differences in drug dosing regimens. For example, dose reduction of abemaciclib is carried out according to the following scheme: 150→100→50 mg. At the same time, the drug is available in all these dosages. A similar picture is characteristic of palbociclib: dose reduction 125→100→75 mg with the same available dosages[3]. Dose reduction for ribociclib is carried out according to the scheme 600→ 400→200 mg with a single dosage of 200 mg (see Fig. 2).

[3] General characteristics of the drug palbociclib. Available from: https://lk.regmed.ru/Register/EAEU_SmPC

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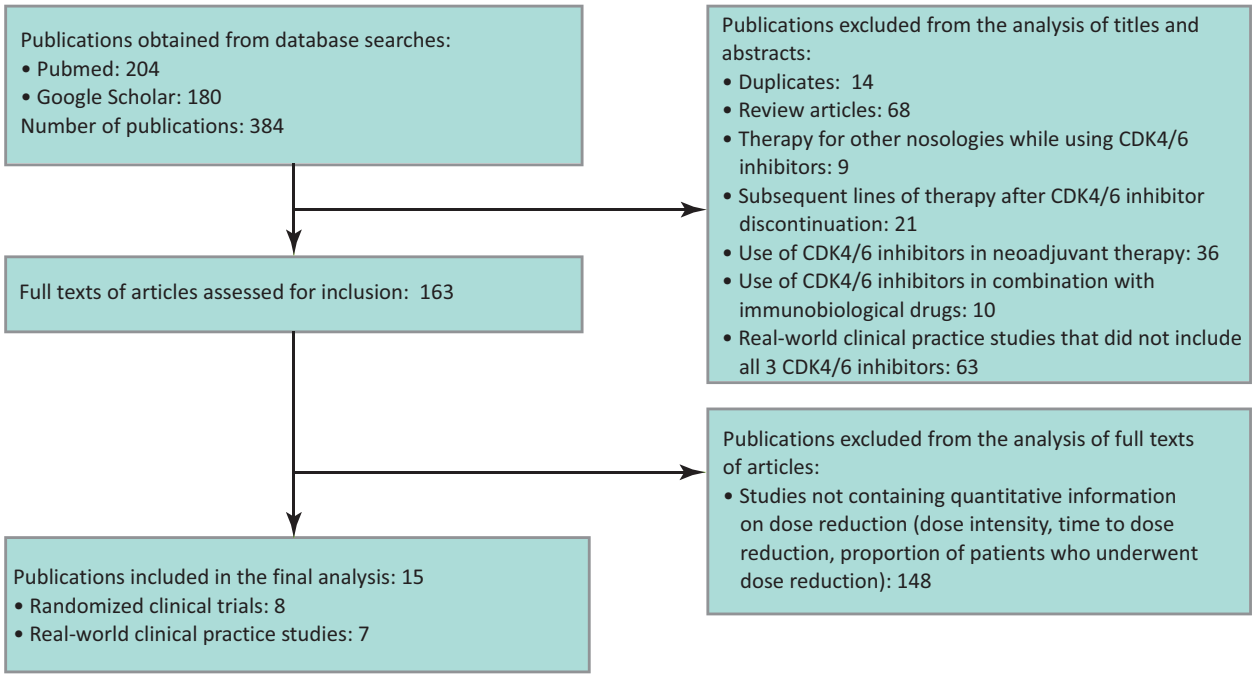

Figure 1 – Publication search strategy.

Table 1 – Dose reduction data extracted from randomized clinical trials

RCT [reference]	Drug and control group, (abs.)	Endocrine partner	Menopausal status	Proportion of patients with dose reduction, % (number of patients)[1]	Median time to first dose reduction, months (min–max)	Proportion of patients with a second dose reduction, % (number of patients)[2]	Median relative dose intensity, % (min–max), drug / placebo[5]
PALOMA-2 [13, 20, 21]	Palbociclib (444) Placebo (222)	Letrozole	Post-	39.4% (175/444)	3.2 (1–28)	36 %) (63/175)	**93.0** (40–110) 99.6 (56–105)
PALOMA-3 [21–23]	Palbociclib (347) Placebo (174)	Fulvestrant	Pre-	42.3% (30/71)	1.2	4.3	**89.8** (22–107) 100 (80–100)
			Post-	31.8% (87/274)			
MONARCH-2 [24]	Abemaciclib (446) Placebo (223)	Fulvestrant	Pre- Post-	42.9% (189/441)3	nd	nd	nd
MONARCH-3 [25]	Abemaciclib (328) Placebo (165)	Anastrozole or letrozole	Pre-	43.6% (142/326)	nd	nd	**86%** 98%
MONALEESA-2 [14]	Ribociclib (334) Palbociclib (334)	Letrozole	Post-	57.4% (192/334)	3.0	40% (77/192)	**65.6% (31.4–99.8%)** 99.3% (50.0–111.9%)
MONALEESA-3 [15]	Ribociclib (484) Fulvestrant (242)	Fulvestrant	Post-	38.7% (92/238)	2.8	17.4% (16/92)	**67.8%** (34.7–99.7%) 98.4% (65.9–131.8%)
MONALEESA-7 [14]	Ribociclib (335) Placebo (337)	Tamoxifen or letrozole or anastrozole	Pre-	37% (91/246)[4]	2.2	27.5% (25/91)	**66.3%** (27.9–98.6%) 98.0% (57.1–104.8%)

Note: RCT — randomized clinical trial; [1] — data is presented in the format — the number of patients who underwent one or more dose reductions and the number of patients who participated in the final data analysis (may not coincide with the total number of randomized patients); [2] — data is presented in the format — the number of patients who underwent a second dose reduction and the number of patients who underwent one or more dose reductions; [3] — the study included patients with both pre- and post-menopause (however, the results do not contain data for each of the subgroups; [4] — the tamoxifen cohort was excluded from the analysis, since the combination with tamoxifen is not registered; [5] — the median relative intensity was calculated as — dose, per patient, divided by the number of days of administration and multiplied by the recommended dosage of the drug.

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Table 2 – Multicenter retrospective real-world clinical practice studies

First author, year [reference]	Number of patients, menopausal status	Dose reduction data[1]		
		Palbociclib	Abemaciclib	Ribociclib
G. Gullick, 2024 [27]	666, pre- and postmenopausal	289/537 (53.8%) • Median cycle number of first dose reduction, *n* (min–max) — 3 (1–63)	50/85 (58.8%) • Median cycle number of first dose reduction, *n* (min–max) — 3 (1–11)	26/44 (59.1%) • Median cycle number of first dose reduction, *n* (min–max) — 2 (1–37)
M. Cejuela, 2024 [28]	206, pre- and postmenopausal	50/96 (52.1%)	30/56 (53.6%)	28/54 (51.9%)
M.M. Queiroz, 2023 [29]	142, menopausal status not specified	34/79 (43%) • Time to first reduction (Me±SD) — 3±8 • Time to second reduction (Me±SD) — 6±5.14	12/21 (57.1%) • Time to first reduction (Me±SD) — 1±2.8 • Time to first reduction (Me±SD) — 17±1.44	18/42 (42.9%) • Time to first reduction (Me±SD) — 2±5.9 • Time to first reduction (Me±SD) — 4±1.54
P. Fedele, 2024 [30]	158, menopausal status not specified	16/57 (28.1%)	19/48 (39.6%)	15/53 (28.3%)
L. Siljander, 2022[4]	2572, menopausal status not specified	Total 1811 Mean relative dose intensity[2] – 0.83	Total 91 Mean relative dose intensity – 0.82	Total 670 Mean relative dose intensity — 0.80
S. Palladino, 2023 [31]	3647, post- and premenopausal	nd/2627 (35%)	nd/291 (44.7%)	nd/729 (22.1%)
K.B. Kristensen, 2021 [32]	128, post- and premenopausal	nd	nd	60/128 (46.8%) • Patients with a second dose reduction — 17/60 (28.3 %)3 • Time to first reduction, Me [min–max] – 2.2 [0.9–17.3] months • Time to second reduction Me [min–max] – 6.5 [1.8–17.5]5

Note: [1] — dose reduction data is presented in the format — number of patients who underwent dose reduction and the total number of patients; [2] — time to second reduction is counted from the start of patient observation; [3] — mean relative dose intensity was calculated as the quotient of the total dose calculated for all patients, divided by the number of days of drug administration, multiplied by the recommended dosage of the drug; [4] — data on the second dose reduction is presented in the format — number of patients who underwent the second dose reduction and the number of patients who underwent dose reduction; [5] — time to second reduction is counted from the start of patient's observation.

Thus, if the dose reduction of ribociclib is multiple and involves reducing the number of tablets with the same dosage per administration, then for abemaciclib and palbociclib, dose reduction requires the use of a new drug package (with a lower dosage[5]). It should be noted that for abemaciclib, in the absence of a dosage for the first dose reduction (100 mg), it can be compensated by taking two 50 mg tablets, which will increase costs, but the therapy regimen will not be violated[6]. In the case of palbociclib, the lack of the required dosage will lead to the cancellation of therapy.

Considering the existing limitations in providing the patient with drugs for anticancer therapy, their availability in the required dosages at any given time may be difficult. Excessive wait time of the patient for the required dosage, or even refusal to take the drug in the initial dosage due to adverse events, or violation of the administration regimen (frequency, rate, etc.) reduces the therapy efficiency. Under this circumstance, the presence of only one dosage in a drug such as ribociclib and the reduction of its dose

[4] Siljander L, Hornemann AT, Møller AH. Real-world relative dose intensity in patients with advanced or metastatic breast cancer treated with cyclin-dependent kinase (CDK) 4/6 inhibitors in Sweden. Presented at the ISPOR Europe Congress 2022, Vienna, Austria and Virtual, 6–9 November 2022. Available from: https://www.ispor.org/docs/default-source/euro2022/isporeusiljander-pdf.pdf?sfvrsn=4e493646_0

[5] General characteristics of the drug ribociclib. Available from: https://lk.regmed.ru/Register/EAEU_SmPC

[6] The State Register of Medicines of the Russian Federation. Instructions for the medical use of the drug abemaciclib. Available from: https://grls.minzdrav.gov.ru/Grls_View_v2.aspx?routingGuid=ca56c862-7110-4a8f-ad46-ecb8008f14f0

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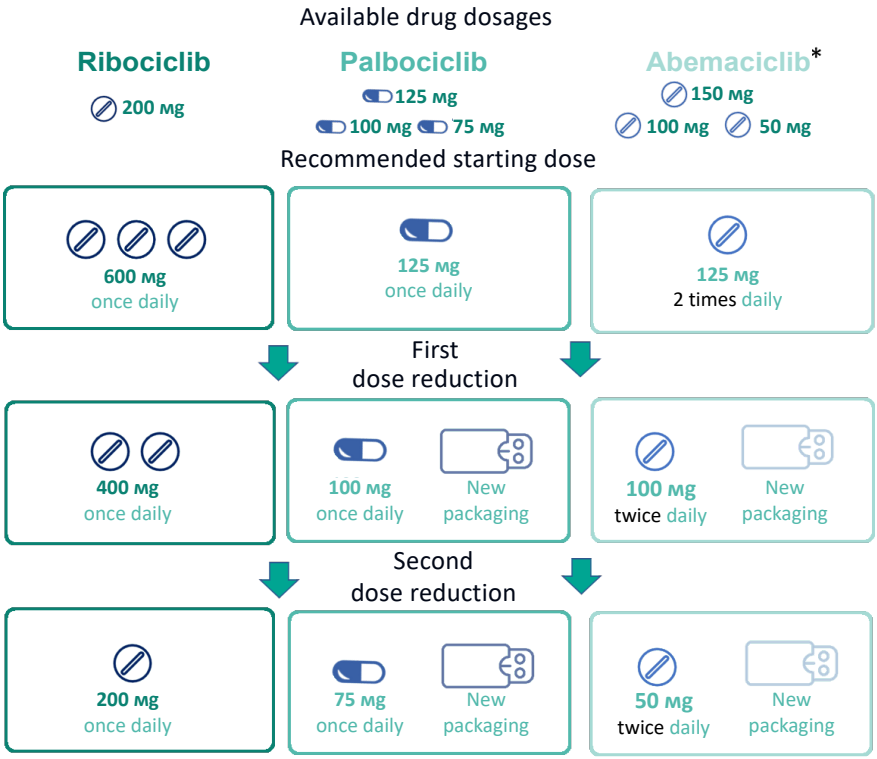

Figure 2 – Use of available dosages of CDK4/6 inhibitors during dose reduction.

Note: * for abemaciclib, the dosing regimen is shown for combining therapy.

by reducing the number of tablets per administration gives it a significant advantage over other CDK4/6 inhibitors in terms of patient adherence to therapy throughout the entire treatment period.

Limitations of the review

Among real-world clinical practice studies, only those studies that included all three CDK4/6 inhibitors — ribociclib, palbociclib, and abemaciclib — were selected. This limitation was introduced to ensure data comparability and focus on modern treatment standards for hormone receptor-positive, HER2-negative metastatic breast cancer, where these three drugs are the main therapeutic options. It is important to note that a significant portion of the studies do not contain detailed quantitative data on dose reduction, despite the fact that the fact of reduction in some patients is indicated in our publication. Variability in approaches to reporting dose reduction data (for example, methods for calculating relative dose intensity or heterogeneity of time intervals for assessing time to reduction) can make it difficult to standardize and compare results between studies. This variability may be due to differences in clinical protocols and patient characteristics, which limits the possibilities for quantitative data synthesis and increases the risk of ambiguity in the interpretation of results.

CONCLUSION

An analysis of data on dose reduction of CDK4/6 inhibitors in the treatment of $HR^+/HER2^-$ breast cancer, published based on the results of RCTs, as well as real-world clinical practice studies, showed that dose reduction is the only way to manage adverse events and is often required by more than half of patients, regardless of the drug chosen. The limited availability of data on the time of onset of the first and second dose reductions, as well as the wide range of values, makes it difficult to predict its necessity in advance, and therefore complicates the process of planning and organizing drug supply. Therefore, from the point of view of rational pharmacotherapy, justifying the choice of a specific drug of this class requires a comprehensive analysis of clinical efficacy indicators, pharmacokinetic parameters, as well as administration features, taking into account the specifics of the healthcare system. A complex process of providing medicines can lead to limited availability of individual drug dosages, which in turn, for example, when a CDK4/6 inhibitor dose reduction is necessary, can lead to a significant decrease in patient adherence to therapy and, accordingly, its effectiveness. In this regard, the presence of a single dosage of ribociclib eliminates potential problems with changing the drug package if a dose reduction is necessary. Based on this, it is necessary to be guided by the principles of

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rational pharmacotherapy and take into account not only the clinical effectiveness of drugs and their tolerability by patients, but also the availability of the entire range of drug dosages, taking into account the upcoming dose reduction, deciding on the appointment of drug therapy with CDK4/6 inhibitors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHORS' CONTRIBUTION

Ilya N. Dyakov — concept development, search and analysis of literary sources, writing a draft of the manuscript;
Sergey K. Zyryanov — concept development, scientific supervision, writing the manuscript.
All authors confirm their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the research, and preparation of the article, read and approved the final version before publication).

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