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CLINICAL CASE REPORTS

HORMONE-POSITIVE HER2-NEGATIVE METASTATIC BREAST CANCER: DECISION MAKING IN REAL CLINICAL PRACTICE

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ABSTRACT

Breast cancer (BC) is the most common female cancer and the first leading cause of cancer death in women. Luminal phenotypes represent about 70% of this disease. Treatment for metastatic hormone-dependent HER2-negative breast cancer in most cases involves various lines of endocrine therapy since their sequential use improves overall and relapse-free survival while maintaining a high quality of life. Disease progression during such therapy may be associated with the development of primary or secondary resistance to the treatment. The reason for the secondary resistance is both a mutation of receptors for steroid hormones and activation of new signaling pathways. The study of these mechanisms has led to the creation of highly effective drug combinations for the treatment of hormone-positive HER2-negative metastatic breast tumors. To date, clinical trials of three agents from the group of cyclin-dependent kinases has been developed and successfully completed: palbociclib, ribociclib and abemaciclib. These agents in combination with non-steroidal aromatase inhibitors or estrogen receptor antagonists in randomized clinical trials increased direct treatment efficacy, overall survival and progression-free survival rates. Clinical case of a menopausal patient with metastatic hormone-positive HER2-negative breast cancer with visceral metastases who received successive chemotherapy and a combination of the highly selective oral kinase inhibitor CDK4\6 ribocyclib with the aromatase inhibitor letrozole allowed to achieve a response to therapy for 27 months with CR for 8 months. The safety profile was satisfactory; side effects included grade 2 neutropenia, grade 1 arthralgia, grade 1 hyperglycemia and grade 1 increase in urea which did not had an adverse effect on the patient's quality of life.

Keywords:
metastatic breast cancer, hormone therapy, cyclin-dependent kinases, ribocyclib, palbocyclib, abemacyclib

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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

ГОРМОНОПОЛОЖИТЕЛЬНЫЙ HER2-НЕГАТИВНЫЙ МЕТАСТАТИЧЕСКИЙ РАК МОЛОЧНОЙ ЖЕЛЕЗЫ: ПРИНЯТИЕ РЕШЕНИЙ В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ

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РЕЗЮМЕ

Рак молочной железы (РМЖ) занимает 1-е место в структуре онкологической заболеваемости и смертности женского населения. Около 70% этой патологии составляют люминальные фенотипы. Лечение метастатического гормонозависимого HER2-негативного РМЖ в большинстве случаев предполагает применение различных линий эндокринотерапии, их последовательное применение обеспечивает увеличение показателей общей и безрецидивной выживаемости при сохранении высокого качества жизни. Прогрессирование заболевания на фоне такой терапии связано с развитием резистентности к проводимому лечению, которая может быть первичной и вторичной. Причинами возникновения вторичной резистентности являются как мутация рецепторов к стероидным гормонам, так и активация новых сигнальных путей. Изучение этих механизмов привело к созданию высокоэффективных комбинаций препаратов для лечения гормоноположительных HER2-негативных метастатических опухолей молочной железы. На сегодняшний день в мире разработаны и успешно завершены клинические исследования трех препаратов из группы циклинзависимых киназ: палбоциклиб, рибоциклиб и абемациклиб. Применение этих препаратов в сочетании с нестероидными ингибиторами ароматазы или антагонистами эстрогеновых рецепторов в рандомизированных клинических исследованиях увеличило показатели непосредственной эффективности лечения, общей выживаемости и частоту выживаемости без прогрессирования. Клиническое наблюдение пациентки с метастатическим гормонопозитивным HER2-негативным РМЖ в менопаузе, с висцеральным поражением, получившей последовательно химиотерапию и комбинацию перорального высокоселективного ингибитора киназ CDK4/6 рибоциклиба с ингибитором ароматазы летрозолом, позволило достигнуть длительности ответа на терапию 27 мес, с достижением полного ответа на лечение, сохранявшегося в течение 8 мес. Профиль безопасности был удовлетворительным, из побочных явлений наблюдались: нейтропения 2 степени, артралгия 1 степени, гипергликемия 1 степени и повышение мочевины 1 степени, что не повлияло отрицательным образом на качество жизни пациентки.

Ключевые слова:
метастатический рак молочной железы, гормонотерапия, циклинзависимые киназы, рибоциклиб, палбоциклиб, абемациклиб

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Breast cancer (BC) is consistently ranked 1st in the structure of cancer incidence and mortality among the female population. BC is a heterogeneous group of tumors. Among all phenotypes, luminal (defined by the expression of estrogen and/or progesterone receptors) HER2-negative tumors predominate, their specific weight can reach 70% [1].

The treatment principles of hormone-dependent HER2-negative metastatic BC have remained unchangeable for several years until nowadays [2]. In 1977, tamoxifen was registered as a drug for the treatment of metastatic BC, and this led to a significant success in the treatment of this disease. After the appearance of aromatase inhibitors in the Arsenal of oncologists and their use in the first line therapy, it was possible to achieve a progression-free survival of 10–13 months (in the case of tamoxifen, it was from 6 to 9 months). The introduction of the next generation drug, fulvestrant, and its use in first-line treatment of metastatic BC increased the median time to progression to 16.6 months compared to 13.8 months for an aromatase inhibitor (anastrozole), as it's demonstrated in the FALCON study [3].

Sequential use of various variants of endocrinotherapy provided a significant increase in overall and relapse-free survival rates while maintaining a sufficiently high quality of life. However, with this tactic, the disease invariably progressed over time. The main reason was the development of resistance to treatment. Tumor resistance to endocrinotherapy can be either primary (initial lack of sensitivity of tumor cells to drug- induced receptor block) or developing during treatment [4, 5].

Secondary resistance may be associated with mutation of the steroid hormone receptors themselves, or by activation of other signaling pathways. The study of these mechanisms eventually led to the development of the latest highly effective drug combinations for the treatment of hormone-positive HER2-negative metastatic breast tumors.

The discovery of the role of cyclin-dependent kinase (CDK) in the regulation of the cell cycle was awarded the 2001 Nobel prize in medicine [6], and eventually led to the creation of the first CDK inhibitor palbociclib, which in combination with letrozole or fulvestrant fundamentally improved the results of hormone therapy for metastatic and locally advanced luminal breast cancer, which was convincingly demonstrated in several multicenter randomized phase II and III studies. Thus, the addition of palbociclib to letrozole in the 1st line of endocrine therapy led to a significant increase in overall survival and immediate effectiveness of treatment, the median progression-free survival was 27.6 months vs. 14.5 months (HR 0.563; 95% CI 0.461–0.687; p<0.000001), and the overall response rate in the entire population was 42.1% vs. 34.7% (p=0.031) [7].

Nowadays, two other drugs have been developed and successfully completed clinical trials in the world: ribociclib and abemaciclib, which were also studied in the first line of therapy for hormone-positive metastatic breast cancer in randomized placebo-controlled phase III trials. The MONALEESA-2 study evaluated the effectiveness of ribocyclib in combination with letrozole, and the median progression-free survival for ribocyclib and placebo was 25.3 and 16 months, respectively (HR 0.568; 95% CI 0.457–0.704; p=9.63 × 10–8). In the subgroup with measurable disease, the combination of ribocyclib with letrozole provided a 52.7% overall response rate compared to 37.1% for placebo with letrozole (p<0.001) [8].

Abemaciclib was studied in the study phase III MONARCH-3, combined with nonsteroidal aromatase inhibitors demonstrated the increased effectiveness of hormone therapy: the median survival without progression in the group with abemaciclib at the time of data collection was not achieved in the placebo group amounted to 14.73 month (OR 0,543; 95% CI 0,409– 0,723; p=0,000021), in the subgroup with measurable lesions abemaciclib combination with anastrozole or letrozole provided the overall frequency response of 59% compared with 44% for placebo (p=0.04) [9].

The FDA has approved the use of all three drugs in both premenopause and menopause,

and ribociclib and palbociclib are registered and available in the Russian Federation. Despite the fact that their clinical effectiveness is almost identical, there are some differences in the toxicity profile, principles of dose reduction, and monitoring during treatment [10].

Clinical Case

Patient P., born in 1959 (58 years old), went to the national medical research center of Oncology (RNIOI) in April 2017 in a good performance status (ECOG 1), complaining of moderate general weakness, decreased performance, and discomfort in the right hypochondrium.

From anamnesis: a tumor in the right breast was discovered in September 2014, and she went to the RNIOI in December 2014, where a comprehensive examination revealed the diagnosis: right breast cancer cT2NxM0 stage II. During a puncture biopsy of the tumor, verification was not obtained. The first stage of complex treatment on 17.12.14 was performed radical mastectomy on the right, histological conclusion was obtained: G2 invasive ductal carcinoma, metastatic lesion of three axillary lymph nodes. The result immunohistochemical expression of estrogen receptors expressed in 80%, expression of progesterone receptors is moderate — 70%, an index of proliferative activity ki67–15%, expression Her2neu — 0. Postoperative diagnosis: right breast cancer pT2N1M0 stage IIB, luminal a subtype. From 23.01.2015 to 14.07.2015, she received 6 courses of adjuvant therapy according to the FAC scheme in standard dosages, a course of remote gamma therapy for postoperative scar and lymph nodes pathways up to 40 Gy of total focal dose. An adjuvant endocrinotherapy with tamoxifen was prescribed, which the patient received further.

In April 2017 the above complaints appeared and she was examined by place of residence. Magnetic resonance imaging of abdominal organs revealed multiple metastases to the liver. The patient was sent to the institute.

During the treatment, a spiral x- ray computed tomography (RCT) of the brain, chest, abdominal cavity and pelvis was performed on 19.04.2017. Multiple metastatic liver lesions were detected up to 5.5 cm, the concretion of the gallbladder up to 2 cm, in the other organs studied without pathological neoplasms. In the biochemical analysis of blood, an increase in the level of transaminases > 3 UNL, a moderate increase in the level of alkaline phosphatase was noted. The clinical data combined with laboratory changes were considered as a visceral crisis.

Thus, based on the examination, a clinical diagnosis was established: right breast Cancer cT-2NxM0 pT2N1M0 stage IIB, complex treatment 2014–2015, generalization in 2017, metastasis to liver. Concomitant diseases: arterial hypertension stage II, cholelithiasis.

Due to the generalization of the disease, the patient underwent 6 courses of chemotherapy (carboplatin and docetaxel in standard dosages) from 22.04.2017 to 15.08.2017. The effect was evaluated every 3 courses. After the 6th course a partial remission was achieved (according to the RECIST criteria). A decrease in the number and size of metastatic leasions in the liver — in the right lobe of the node up to 1.4 cm, in the left lobe — up to 2.7 cm) was found. In the biochemical blood analysis, the level of transaminases and alkaline phosphatase was normalized comparing to the beginning of the treatment. The therapy was accompanied by toxicity in the form of grade II nausea, grade I–III leukopenia, grade III neutropenia, grade I–II peripheral sensory neuropathy, and grade 2 alopecia. The Patient also found an improvement in general well-being, but general weakness persisted.

Since 19.09.2017, in order to continue the effect achieved after chemotherapy, antitumor drug therapy was started according to the scheme: ribociclib 600 mg per day inside for 1–21 days, a break up to 28 days, letrozole 2.5 mg per day p. o. continuously, 24 cycles were performed, and treatment continued until 08.07.2019.

The therapy tolerability was satisfactory, the following side effects were noted comparing to the beginning of treatment: neutropenia 2 gd,

during treatment was recorded three times, for the first time in 9 months from the beginning of ribociclib therapy, lasting 5, 4 and 1 month, which did not require the cancellation or reduction of the dose of ribociclib. Arthralgia 1 gd. with damage to the joints of the hands and feet, after 12 months of hormone therapy. Alopecia 1 gd. appeared after 9 months of treatment with ribociclib and persisted throughout the whole treatment period. From laboratory abnormalities, hyperglycemia 1 gd., developed in 18 months after the start of therapy, which lasted for 3 months, and an increase in urea of 1 gd was sound in 19 months after the start of treatment. Adverse effects didn't affect the patient's quality of life. ECG was performed monthly and significant changes, including the QTc interval, were not revealed.

Every 12 weeks, the effectiveness of the therapy was evaluated according to the RECIST criteria.

During 14 months, the disease remained stable according to CT control, and the control measurable leasions decreased by 30% from the initial ones, the next CT control performed on 16.11.2018, discovered complete remission — metastatic leasions measurable and immeasurable in the liver were not visualized, there were no new metastatic leasions in organs and systems. The complete response continued for 8 months. In July 2019, control CT revealed the progression of the disease. Response to the treatment with the use of letrozole and ribociclib and maintained for 22 months. The duration of response to treatment with chemotherapy followed by the appointment of a CDK 4/6 inhibitor with letrozole was about 27 months.

CONCLUSION

The use of cyclin-dependent kinase inhibitors (CDK 4/6) is a new option in the treatment of hormone — positive HER2-negative metastatic BC. The article presents a clinical case of a patient with hormone-positive HER2-negative BC in menopause, who after complex treatment and endocrinotherapy with tamoxifen in 2 years revealed the progression of the disease with multiple metastatic liver damage and visceral crisis development. The administration of chemotherapy followed by the use of a combination of the oral highly selective CDK4\6 kinase inhibitor ribocyclib with the aromatase inhibitor letrozole allowed to achieve a duration of response to therapy of 27 months, with the achievement of a complete response to treatment within 8 months.

The tolerability of therapy was satisfactory and well-managed, during the treatment, the symptoms of the disease were stopped and the quality of life was improved.

Based on the information above, it can be concluded that the use of cyclin-dependent kinase inhibitors in real clinical practice is the optimal therapy option for patients with metastatic hormone -positive HER2-negative BC.

Authors contribution:

Vladimirova L.Yu. – research concept and design, text writing, scientific editing, data collection, analysis and interpretation, article preparation.

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