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CLINICAL OBSERVATION OF THE USE OF ORAL VINORELBINE IN THE TREATMENT OF DISSEMINATED ESTROGEN-RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER.

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Abstract:

Fresh water supply is a major challenge to agriculture in semi-arid zones and deep groundwater pumping for irrigation is applied widely in such regions to span droughts. However, climate change and overexploitation of groundwater reservoirs foster instability and qualitative degradation of aquifers, thus adaptation measures to increasing water scarcity such as the construction of fresh water reservoirs from surface runoff were applied during the last decades. Small-scale retention basins seem to be ecologically more appropriate in comparison to large dam systems, as construction of large dams causes deforestation and harmful impacts on wildlife. In this context, the ways of controlling and monitoring of water will be discussed

Keywords: Breast Cancer, Disseminated, HER2-Negative, Estrogen

INTRODUCTION

Drug treatment of disseminated estrogen receptor-positive (RE+), HER2-negative breast cancer (BC) is currently the concept of chronic disease therapy. The main goals of drug therapy are to control the symptoms of the disease, as well as to ensure the highest quality of life for the patient. For this category of patients at the first stage of therapy, the most rational approach is to conduct sequential lines of hormone therapy. At the same time, combinations including inhibitors of cyclin-dependent kinases (CDK) 4 and 6 are the standard of the 1st line of therapy [1]. Subsequent lines of hormone therapy may include everolimus, as well as alpelisib for patients with a PIK3CA mutation [2, 3].

Patients with BRCA1/2 germline mutations can be allocated to a separate group of ER+, HER2-negative breast cancer. For this group of patients, an effective treatment option after the exhaustion of reserves of hormone therapy is therapy with poly(ADP-ribose) polymerase (PARP) inhibitors. Olaparib and talazoparib have a similar toxicity profile - the most common type of hematological toxicity is anemia, which reaches grade 3 in 30% of cases [4, 5].

For patients who have previously received chemotherapy with the inclusion of taxanes and anthracyclines, including in the adjuvant regimen, today there is no "gold standard" of first-line chemotherapy. According to the recommendations of the European Society for Medical Oncology, monochemotherapy with one of the following drugs is possible: vinorelbine, capecitabine, eribulin, gemcitabine. With a long interval after taxane therapy, a return to this group of drugs is possible [1]. The use of combined regimens in the treatment of disseminated EC+, HER2-negative BC did not demonstrate a significant increase in survival rates, but turned out to be significantly more toxic than monochemotherapy [6]. Combination therapy can only be considered in the clinical situation, when it is necessary to achieve a rapid objective response and is used mainly in the triple negative variant of breast cancer.

Oral chemotherapy can improve the quality of life of patients, while ensuring high efficiency of the treatment. The use of oral vinorelbine as the 1st line of chemotherapy in patients with non-visceral prevalence of EC+, HER2-negative breast cancer after the exhaustion of hormone therapy reserves allows achieving long-term stabilization of the disease (more than 24 weeks) in 51% of patients. At the same time, the median duration of treatment with oral vinorelbine was 5.8 months, the median progression-free survival was 8.2 months. (95% confidence interval (CI) 5.5–9.8 months), and the average duration of clinical efficacy was 10.9 months. (95% CI 8.6–14.7 months). The most common grade 3 and 4 adverse event was neutropenia, which developed in 38% of patients, and no cases of febrile neutropenia were recorded. In the spectrum of non-hematological toxicity, the development of arthralgia of the 3rd degree was most often noted [7]. In addition, the use of oral cytostatic agents has significant advantages in terms of ease of use and the possibility of prescribing in a wider outpatient practice. According to a survey of patients, it was demonstrated that the majority prefer oral therapy over intravenous drugs, provided that the effectiveness of treatment is absolutely equivalent [8].

A review of data from more than 2000 patients treated with anthracyclines and taxanes and treated with

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capecitabine or vinorelbine monotherapy showed the effectiveness of these chemotherapy drugs, which provide average disease control rates (overall response plus stabilization) of approximately 55% and 50%, respectively [9]. A comparative prospective randomized phase 2 study also showed comparable efficacy of these drugs (Table 1) [10].

CLINICAL OBSERVATION

Patient K., 37 years old. In May 2005, she discovered a nodular formation in the left breast. According to ultrasound data, the nodule is 18×16 mm. On November 10, 2005, a sectoral resection of the left breast was performed, according to the data of a planned histological examination - "invasive adenocarcinoma of nonspecific type II stage of malignancy." On November 12, 2005, a radical subcutaneous mastectomy was performed on the left with simultaneous reconstruction with an implant. Histological examination showed a microfocus of cancer in the projection of the scar in the breast tissue, in 2 of 11 lymph nodes there were breast cancer metastases with signs of extranodal invasion. From 31.01.2006 to 10.05.2006, 5 courses of adjuvant chemotherapy were performed according to the CAF scheme. Next, adjuvant external beam radiation therapy (EBRT) was performed on the area of the left mammary gland and the zone of regional lymphatic drainage. Adjuvant hormone therapy with tamoxifen 20 mg/day against the background of ovarian suppression with goserelin 3.6 mg once every 28 days was completed in 2011. In March 2015, the patient noted the appearance of periodic pain in the projection of the sternum, as well as pain in the sacrum associated with movement . According to the PET-CT data of April 27, 2015, an increase in specific metabolic activity was revealed in the soft tissues of the anterior chest wall on the left, in the body of the sternum, as well as in the S1 body with a transition to the lateral masses of the sacrum.

On April 18, 2015, the excision of the intradermal metastasis was performed in the projection of the postoperative scar. Histological examination revealed invasive adenocarcinoma of a nonspecific type, RE 6b, RP 8b, HER2/neu — 0, Ki67 — 20%. On May 8, 2016, 1st-line hormone therapy with tamoxifen 20 mg/day, zoledronic acid therapy 4 mg once every 28 days was started. From 06/17/2015 to 06/30/2015, palliative EBRT was performed on the sacral region ROD 3 Gy, SOD 30 Gy. Examination in August 2015 revealed stabilization of lesions in the bones. She continued therapy with tamoxifen and zoledronic acid. Examination in April 2016 revealed stabilization of foci in the bones, progression due to the appearance of a lesion in C7 of the liver up to 10 mm and in C4 17 × 12 mm. Since April 2016, ovarian suppression with goserelin 3.6 mg s.c. once every 28 days has been started; since May 2016, letrozole 2.5 mg/day has been added to therapy; continued therapy with zoledronic acid. During the examination in July 2016, the growth of the focus in C7 of the liver up to 15 mm, in C4 - up to 28 × 14 mm, the appearance of a new focus in C4 up to 3 mm. Taking into account the absence of complaints in the patient, as well as the absence of deviations in the biochemical blood test, hormone therapy of the 2nd line with aromatase inhibitors was continued. According to ultrasound data in September 2016, a decrease in the size of foci in the liver: in C7 up to 9 mm, in C4 up to 20 × 10 mm; 2nd line hormone therapy continued.

In July 2017, progression was noted in the form of an increase in the size of the metastatic focus in C7 of the liver up to 32 × 18 mm. Stabilization of metastatic foci in the bones. Since July 2017, 3rd-line hormone therapy with fulvestrant 500 mg IM was started on days 1, 15, 28, then once every 28 days; since September 2017, palbociclib 125 mg/day orally in 1 -21st day of a 28-day cycle. During therapy with palbociclib, the development of dose-limiting neuropenia was noted, which required dose reduction to 100 mg/day from the 3rd course of therapy. According to the control examination in December 2017, the lesions in the liver and bones were stabilized.

A follow-up examination in May 2018 revealed new lesions in the liver. In the biochemical analysis of blood, an increase in the activity of transaminases up to 2 norms. In order to achieve stable ovarian suppression, bilateral laparoscopic oophorectomy was performed on June 22, 2018. Since June 2018, 4th-line hormone therapy has been started according to the scheme: exemestane 25 mg/day + everolimus 10 mg/day daily. According to the control survey in September 2018 - stabilization. In December 2018, the appearance of tumor-associated fever was noted, according to the control examination, the growth of foci in the liver, the largest foci in S5 up to 56 mm.

Since December 2018, oral chemotherapy with capecitabine 2000 mg/m2 of body surface area has been started on days 1–14 of a 21-day cycle. During the control examination in March 2019, a partial regression of foci in the liver was noted. Toxicity of therapy - hand-foot syndrome of the 3rd degree, in connection with which, from the 5th course, the dose of capecitabine was reduced by 1 dose level (by 25%). On the background of capecitabine therapy, stabilization of foci

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in the liver was noted, subsequent dose reduction (up to 1500 mg/m2 of body surface area) due to hand-foot syndrome of the 3rd degree was carried out from the 10th course of therapy. Progression in March 2020 - an increase in the size of lesions in the liver. In the biochemical blood test, an increase in transaminase activity up to 3 norms was noted. A core biopsy of the lesion in the right lobe of the liver was performed, according to the immunohistochemical study — RE 7b, RP 5b, HER2/neu — 0, Ki67 — 40%, PIK3CA mutation was detected.

Since March 2020, therapy with oral vinorelbine 60 mg/m2 of body surface area was started on days 1, 8, and 15. Due to satisfactory tolerability from the 2nd course of therapy, the dose of vinorelbine was increased to 80 mg/m2 of body surface area. According to the control examination in June 2020, stabilization of foci in the liver was revealed, as well as the normalization of biochemical blood test parameters. Reducing the dose of vinorelbine to 60 mg/m2 of body surface area from the 5th course was carried out in connection with the development of dose-limiting neutropenia of the 3rd degree. In February 2021, progression of the disease was noted: an increase in the size of foci in the liver, an increase in transaminases up to 2 norms, pain in the right hypochondrium of the 2nd degree. Since February 2021, chemotherapy has been started according to the scheme: eribulin 1.4 mg/m2 of body surface area on days 1 and 8 of a 21-day cycle. The treatment was complicated by the development of grade 3 sensory polyneuropathy after the 3rd course of therapy, which required the withdrawal of eribulin. According to the control survey in April 2021 - stabilization. Taking into account the intolerable toxicity of the previous line of therapy, since May 2021, hormonal therapy with fulvestrant 500 mg on days 1, 15, 28, then once every 28 days, alpelisib 300 mg/day orally has been started. Due to the development of grade 3 skin toxicity, the dose of alpelisib was consistently reduced to 200 mg/day (Fig. 1). According to the control examination in August 2021 - stabilization of foci in the liver. The patient continues therapy with a combination of fulvestrant and alpelisib.

On the example of this clinical case, we see that with the rational appointment of consecutive lines of hormone therapy, it is possible to postpone the start of chemotherapy of the 1st line by 3.5 years and maintain a satisfactory quality of life for the patient. In the case of treatment of disseminated ER+, HER2-negative breast cancer, we can discuss such a surrogate indicator of treatment effectiveness as the time before the start of intravenous chemotherapy. In the case of this patient, oral chemotherapy made it possible to control the disease for 26 months. with minimal impact on the patient's quality of life. The oral form of vinorelbine as monotherapy is the optimal method of treatment in patients whose main goal of treatment is to control a slowly progressive disease, or in patients who are resistant to hormone therapy. Weekly oral administration of vinorelbine is a simple and convenient method of treatment while maintaining a high quality of life in such patients [11]. In addition, in the context of the COVID-19 pandemic, which implies limited visits to medical institutions, oral chemotherapy, in particular vinorelbine capsules, can be considered as the therapy of choice for such patients.

CONCLUSION

Thus, when planning the next treatment regimen for patients with disseminated EC+, HER2-negative breast cancer, we, first of all, should take into account the expected toxicity of therapy, the toxicity of previous treatment, as well as the patient's opinion regarding her readiness to visit the clinic for intravenous infusions, assess the impact of the expected toxicity on the patient's quality of life.

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