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MODERN METODE TREATMENT CASTRATION-REFRACTORY PROSTATE CANCER

Resume: Long-term treatment in patients with castration-refractory prostate cancer was extremely symptomatic and quality of life and overall survival were low. In the 2000s, investigations aimed at designing drugs to treat this category of patients were underway, which have culminated in the advent of three drugs (two of which belong to chemotherapy) that are now used in the world.

Key words: castration-refractory prostate cancer, intracrine synthesis of testosterone, hypersusceptibility of tumor receptors, hyperproduction of tumor receptors.

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МЕТОДЫ СОВРЕМЕННОЙ ТЕРАПИИ КАСТРАЦИОННО-РЕФРАКТЕРНОГО РАКА ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ

Резюме: Длительное время лечение пациентов с кастрационно-рефрактерным раком предстательной железы являлось исключительно симптоматическим, а качество жизни и общая выживаемость были невысокими. В 2000 годах начались исследования, направленные на разработку препаратов для данной категории пациентов, завершившиеся появлением 3 лекарственных средств (2 из которых относятся к химиотерапии), в настоящий момент применяемых в мире.

Ключевые слова: кастрационно-рефрактерный рак предстательной железы, интракринный синтез тестостерона, гиперчувствительность опухолевых рецепторов.

Introduction: Currently, hormone therapy (GT) is the main method in the treatment of patients with disseminated prostate cancer. The use of androgen-deprivation therapy is an effective method of drug exposure in more than 90% of patients, however, the average time to disease progression after GT in patients with metastatic prostate cancer is about 2 years [1,2]. Patients who have a progression of the tumor process against the background of a persistent castration level of testosterone, go into the stage of the so-called castration-resistant prostate cancer (CRPC). In addition, in some patients, the tumor is initially resistant to hormonal effects. The average life expectancy of patients in this group is about 6-12 months. Widespread CRPC is not only a prognostically unfavorable disease, but also significantly worsens the quality of life of patients and requires regular systematic examination and monitoring of the patient [3, 4].

According to modern concepts, the criteria for CRRF are considered to be the progression of the disease (an increase in the level of prostate-specific antigen (PSA) or progression according to radiological examination) against the background of castration levels of testosterone in the blood serum (testosterone <50 ng/dl or <1.7 nmol/L) [14]. Radiological assessment is carried out using the RECIST and PCWG2 criteria, according to which the progression of the disease is considered to be the appearance of ≥2 new unmeasurable foci in bones according to bone scans or an increase in the size of the sum of the diameters of the measured tumor foci ≥20% of the original size, or the appearance of new foci [1,5].

After the GT, few treatment regimens are active with the progression of the process. Currently, the use of cytostatic drugs remains the standard method of therapy for patients with CRPC [5]. At the same time, advances in molecular biology have led to a detailed understanding of the mechanisms underlying the

development of castration refractoriness. The loss of dependence of tumor cells on testosterone concentration may have several mechanisms, such as mutation of androgen receptors, overexpression of androgen receptors as a result of gene amplification, stimulation of receptors by growth factors and protein kinase activators. In this regard, it is possible to use various therapy options aimed at pathogenetic mechanisms of hormonal resistance development for the treatment of CRPC: cancellation or replacement of antiandrogens; prescribing drugs that block the synthesis of adrenal androgens; the use of large doses of antiandrogens; therapy with growth factor inhibitors and protein kinases; vaccine therapy; systemic radiopharmaceutics. Taking into account the fact of the presence of a metastatic process and bone tissue damage in most patients with CRPC with the presence of pain syndrome and the risk of developing bone complications, concomitant therapy with bisphosphonates, RANKL ligand inhibitors, and symptomatic radiation therapy is possible [6].

Despite the development of castration resistance and the progression of the disease against the background of GT, all patients with CRRPJ need to continue castration therapy by performing surgical or drug castration. The expediency of maintaining the castration level of testosterone in patients with CRPC throughout the entire period of further therapy is justified by the result of a number of large randomized studies. Thus, in a study involving 87 patients with CRPC, in whom the progression of the disease was noted against the background of surgical castration performed earlier, the effectiveness of chemotherapy using an inhibitor of the synthesis of adrenal antiandrogens aminoglutetimide in combination with prednisone was evaluated [7]. The patients were randomized into a group of patients who were additionally prescribed androgen stimulation and a control group. The results of the study showed that in the subgroup of patients who were prescribed additional stimulation with androgens, the overall survival was significantly lower than in the control group, and was 10 and 15 months, respectively (p=0.0047).

Another retrospective study, which included 341 patients with CRPC, also demonstrated the importance of continuing castration therapy in this cohort of patients. The duration of androgen deprivation was an independent prognostic factor affecting the overall, relapse-free and tumor-specific survival rates of patients [5,6].

The purpose of the study. To improve the results of treatment of patients with mCRRPJ using modern schemes based on docetaxel and abiraterone acetate.

Materials and methods of research. General characteristics of the clinical material . The study analyzed the medical histories of 83 patients of mCRRPJ who were treated at the ASMI clinic from 2020 to 2021.

The results of the study. The docetaxel-abiraterone treatment regimen significantly increases the overall survival of patients compared to the abiraterone-docetaxel regimen (median of 30.4 months versus 26.3 months p=0.01), patients who responded to hormone therapy for more than 12 but less than 18 months with a process stage of no more than T2N1M0, normal laboratory parameters, ECOG status and having pain syndrome may be recommended both the docetaxel-abiraterone regimen and the abiraterone-docetaxel due to the absence of significant differences in overall survival (p>0.05).

Docetaxel-abiraterone treatment regimen significantly increases progression-free survival compared to abiraterondocetaxel regimen (median of 25.9 months vs 19.9 months, p=0.002)

Treatment regimens have a comparable frequency of side effects. The most clinically significant complication is the development of neutropenia, which occurred in 26.5% of patients with the use of docetaxel, while for abiraterone, the main side effects were the phenomena of mineralcorticoid toxicity - hypokalemia, swelling, increased blood pressure.

The factors of unfavorable prognosis of patients with MCRPH are the presence of metastatic lesion of regional lymph nodes, the presence of severe pain syndrome requiring the use of narcotic analgesics, ECOG 1-2 status, duration of previous hormonal therapy less than 18 months, hemoglobin level less than 120 g/l, the level of alkaline phosphatase before treatment is above 1.5 VGN (180 U/l), an increase in the level of alkaline phosphatase during treatment above VGN (120 U/l), LDH level before treatment is above 2 VGN (500 units / l), the PSA level at the time of establishment of castration refractoriness is above 30 ng/ml; PSA level before the start of line 2 therapy is above 90 ng/ml; PSA nadir during line 1 and 2 therapy is above 28 ng/ml and 60 ng/ml, respectively ($p<0.05$);

Factors that significantly affect the decrease in progression–free survival are the presence of metastases to regional lymph nodes, ECOG 1-2 status, duration of hormone therapy less than 18 months, PSA at the time of establishment of castration refractoriness less than 30 ng/ml, hemoglobin level less than 110 g/ l, the level of alkaline phosphatase and LDH above the upper limit of normal, PSA decrease by less than 50% during line 1 and 2 therapy, PSA before line 2 therapy more than 90 ng/ml, nadir during therapy 1 lines less than 28 ng/ml, against the background of therapy 2 lines - less than 60 ng / ml ($p <0.05$).

Conclusion. The use of chemotherapy is associated with the development of hematological toxicity, including neutropenia of varying severity, in some cases requiring maintenance therapy with HCF, therefore it is necessary to strictly monitor the temperature reaction and general blood test in patients after treatment, as well as timely prescribe maintenance therapy.

The use of abiraterone acetate is associated with a worsening of the severity of hypertension, therefore, patients receiving abiraterone therapy should monitor blood pressure levels even in the absence of hypertension before starting therapy.

In the absence of signs of clinical and/or radiological progression, it is advisable to continue the treatment even against the background of continued **growth of PSA**

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