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Modern Approaches to the Treatment of Castration-Resistant Prostate Cancer

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Abstract:

In the treatment of metastatic hormone-resistant prostate cancer, the use of chemotherapy both in single mode and in combination with other drugs is currently the standard. In most cases, prostate cancer responds well to hormonal androgen deprivation therapy (therapeutic castration). Unfortunately, over time, in many patients, the tumor begins to progress, despite ongoing treatment. A decrease in testosterone levels becomes insufficient to keep the growth of malignant cells. This condition is called hormone-resistant, hormone-refractory, or castration-resistant prostate cancer. The search for drugs, their combinations and new treatment regimens for patients with GRP continues in order to improve treatment results.

Keywords: prostate cancer, chemotherapy, castration-resistant, median survival.

Introduction. The right approach allows you to prolong and improve the quality of life of the patient. However, despite the active search in this direction, many clinical studies have not yet allowed us to make big breakthroughs and significantly improve treatment results. After the publication of the results of studies of TAX 327 and SWOG 9916 [1, 2], chemotherapy (CT) with Taxotere (docetaxel) is the 1st line and standard of treatment for metastatic hormone—resistant (GR) prostate cancer (prostate cancer) - GRPJ. Most researchers recognize that hormone resistance is a heterogeneous disease, and although there is a standard today, there are quite a lot of questions about the treatment of this pathology, which in the literature and discussions at symposiums are designated as "what?", "when?", "to whom?". In metastatic GRPJ, docetaxel CT is usually

performed after diagnosis. In the case of detection of hormone resistance of a non-metastatic nature (biochemical progression), the above questions arise. An even more difficult situation develops with the development of biochemical or clinical progression in patients treated with docetaxel. The question arises: what to do next? The second line has not yet been determined. Is it necessary to transfer the patient to symptomatic treatment, or is there still an opportunity to continue specific drug therapy? These problems will be the subject of discussion in this article. Treatment of advanced prostate cancer remains palliative to date. Androgen deprivation in 70-80% of patients with metastatic prostate cancer leads to symptomatic improvement within 18-24 months and a decrease in the level of prostate-specific antigen (PSA), but subsequently patients develop hormonal resistance. Attempts to use the 2nd line of hormone therapy (GT) contribute to achieving a short period of remission in only a part of patients. Subsequent progression leads to a fatal outcome with a median survival rate of 12 months [1, 2]. Should patients with asymptomatic advanced prostate cancer receive docetaxel treatment? To date, there is no convincing answer to these questions in the literature. There are arguments for and against. The use of CT in the initial stages of the disease does not yet contribute to an increase in survival, however, it can lead to the development of toxicity and the onset of earlier drug resistance. Apparently, before the appearance of an effective 2nd line of HT, docetaxel should be used taking into account the individual course of the disease. Prior to the publication of the analysis of the TAX 327 study, a number of recommendations were made based on the opinion of experts. Mandatory follow-up was proposed in asymptomatic patients with a slow time of doubling of the PSA index. Patients with symptomatic metastases only in the bones and a slow doubling time of the PSA value were recommended to undergo secondary GT with ketoconazole in combination with zometa and palliative radiotherapy (LT). In patients with rapid growth and a high rate of doubling of PSA levels, the presence of symptoms and/or visceral metastases, docetaxel-based CT was indicated. The clinical forms of GRPJ vary depending on the presence or absence of symptoms and metastases. In this regard, patients can be divided into 4 categories [3]: 1) an increase in PSA levels is only a biochemical progression; 2) asymptomatic metastases are a limited lesion; 3) asymptomatic metastases are widespread; 4) symptomatic metastases. The table shows indications for CT in various groups of patients with GRPJ, which once again confirm the fact that GRPJ is a heterogeneous disease. To date, the question of where to start treatment of asymptomatic patients remains open. It remains debatable whether it is necessary to carry out the 2nd GT line or it is better to start HT. Further clinical studies are needed to confirm and resolve this issue. Another equally important question is whether to start CT in men with minimal manifestations of symptoms or wait until a more vivid manifestation of the clinical picture on the part of metastases. It should be taken into account that during docetaxel treatment, clinical reduction of symptoms is less common than a decrease in PSA [1]. Patients without pain are better able to tolerate 10 cycles of CT than those with pain syndrome. In this regard, it is advisable to prescribe CT in cases where symptoms develop and / or increase, as well as in the absence of the latter, if there is a high risk of developing negative clinical manifestations in the near future. In such situations, it is necessary to base on the time of doubling the PSA indicator. The results of the study of TAX 327 showed that when using Taxotere in asymptomatic patients, the median survival was 21.3 months, while in patients with various symptoms it was 14.2 [4]. In addition, it should be remembered that the early use of HT by docetaxel can lead to a deterioration in the quality of life. Despite the fact that in the study of TAX 327, the quality of life in general was significantly better with the use of Taxotere than with the use of mitoxantrone [1], in a subgroup of patients with minimal symptoms, especially with weekly administration of docetaxel, a deterioration in the quality of life was noted [5]. This important point should also be taken into account and discussed with patients when drawing up a treatment plan. At this stage, there is no clear answer about the timing, i.e. when and in what situations docetaxel HT should be started. A retrospective multivariation analysis was performed and models based on the clinic, the dynamics of the PSA level and independent prognostic factors used to assess the prognosis of survival for 1, 2 and 5 years in the treatment with Taxotere were created [6]. Clinical signs were also taken into account: the

presence of pain at the beginning of the study, the initial PSA level, age, type of progression relative to the initial status (the appearance of measurable formations or new foci during bone scanning), the presence of liver metastases and the number of metastatic foci. A.J. Armstrong et al. [6] performed a retrospective analysis of the dynamics of PSA levels, during which a significant improvement in survival was revealed in patients with an initial PSA value < 114 ng/ml and a doubling time of 55 days. In a study conducted by S. Oudard et al. [7, 8], the importance of the kinetics of PSA level and pain syndrome in patients with GRPJ was confirmed. The median survival rate of patients who had a doubling of the PSA index for > 45 days and had no pain syndrome was 32.4 months. In the group of patients whose PSA doubling time was < 45 days and intense pain occurred, the median survival was only 8 months. The importance of PSA level kinetics is also confirmed in other studies [9, 10] as the most important prognostic factor. Therefore, a necessary condition in the treatment tactics of patients with GRPJ is to determine the kinetics of PSA levels, especially in the absence of clear indications for docetaxel CT, including in asymptomatic patients or patients who have only progression in PSA. Assessment of the kinetics of PSA content helps to inform the patient and his relatives about the prognosis of the course of the disease and the expected positive effect that the use of CT can give. In addition, in the presence of most unfavorable prognostic factors for the course of the disease and a very short time for doubling the PSA level, the use of docetaxel contributes only to a slight increase in life expectancy, and also affects its quality. Thus, HT with a Taxotere is the only method of treating patients with GRPJ. However, the issue of the start time of treatment is still controversial. In the case of GRPJ without metastases with slow progression of PSA levels, it is possible to use the 2nd line of GT. The decision on the appointment of docetaxel in this category of patients is made individually, taking into account the initial PSA index and the time of its doubling.

Materials and methods. Patients with metastatic GRPJ and the presence of bone progression should receive Taxotere therapy with its administration every 3 weeks. Repeated treatment with Taxotere To date, intensive studies are being conducted to study the further treatment of patients with GRP in the event of discontinuation of docetaxel therapy. Some patients stop treatment due to the progression of the disease, the development of severe toxicity (III–IV degree) or obtaining the maximum favorable response to the therapy. The duration of treatment with Taxotere in case of achieving a positive effect from the start of treatment has not been determined today. In the case of progression after the use of docetaxel, only mitoxantrone is approved as a drug, the appointment of which can give a palliative effect. When used in the 2nd line after docetaxel therapy, the achievement was short 24 (3-37) months, the average observed survival was 15.3 (3-32). The main side effects that occurred after repeated administration of docetaxel were leukopenia, alopecia and fatigue. None of the patients interrupted therapy earlier than scheduled. There are reports of the use of docetaxel in the 2nd and 3rd lines of therapy in patients with metastatic GRPJ. J. Ansari et al. [17] presented data on 107 patients who received docetaxel + prednisolone at a 3-week interval in the 1st line of treatment. The average initial PSA value was 185 (6.6–2000) ng/ml. Of this group, 22 patients were subsequently treated with the 2nd and 7 with the 3rd line of HT with docetaxel. The number of cycles performed in lines 1, 2 and 3 was 650, 119 and 38, respectively. 59% of patients from the entire cohort responded to primary docetaxel therapy. Positive results (a decrease in PSA levels >50%) were obtained in 90 and 71% of the initially responding patients after the 2nd and 3rd administration of the drug, respectively. The development of grade III–IV neutropenia in lines 1, 2 and 3 was registered in 2.9; 4.2 and 5.2% of cases, respectively. The median survival rate was 15.9 months. The data from the above studies have demonstrated the possibility of repeated use of Taxotere in patients who have received a response to the 1st line of therapy. The primary resistance to docetaxel and the subsequent choice of treatment remains a problem, since the definition of the 2nd line of CT is the subject of a search. Combinations with both new cytostatics and targeted drugs are being studied. R. Epplen et al. [18] studied the effectiveness of using a combination of docetaxel with bevacizumab in the 2nd line of therapy in 23 patients with progressive PSA after taking

docetaxel in the 1st line. The median relapse-free period after the 1st line of therapy was 6.2 (3-11) months. The time of doubling of the PSA content before the start of the 2nd line was 5.9 (2-8) months. Docetaxel was administered weekly at a dose of 35 mg / m2, bevacizumab – 10 mg / kg once every 2 weeks. The PSA content before the start of the 2nd line of treatment averaged 189.4 (95-1200) ng/ml. 16 (69.5%) patients showed a regression of PSA levels by more than 50%. With an average follow-up period of 29 months, the median survival rate was 17.5 (3-32) months. The development of hypertension due to the administration of bevacizumab was registered in 21.7% of cases. One patient was excluded from the study due to the occurrence of severe proteinuria due to taking the drug. The authors emphasize that the use of a combination of docetaxel and bevacizumab in the progression of HRT in patients is tolerated satisfactorily and can serve as a method of choice in the case of a rapid doubling of PSA levels noted after the 1st line of docetaxel treatment. A. Heidenreich et al. [19] presented data on the use of a combination of docetaxel + bevacizumab in comparison with repeated administration of docetaxel. Progression after docetaxel therapy was noted in 59 patients. The patients were divided into groups: in the 1st, docetaxel was re-administered at a dose of 35 mg/m2 weekly for 3 weeks, the 4th week was a break; in the 2nd, docetaxel at a dose of 25 mg/ m2 with a weekly interval and bevacizumab - 10 mg / kg with a 2—week interval. In all patients who received the 1st line of therapy, a decrease in PSA levels of > 30% was recorded. In general, after the 2nd line, a decrease in the PSA index of > 30% was noted in 40 (67.8%) of 59 cases in the entire group. Recurrence-free survival in group 1 was 6.2 months, total — 13.3 months, in group 2 - 8.9 and 17.5 months, respectively. The toxicity associated with the administration of bevacizumab in the form of hypertension was observed in 17.8% of patients.

In 1 patient, treatment was discontinued due to the development of high-grade proteinuria. The SWOG 9916 protocol studied the use of a combination of docetaxel + estracite in the 1st line of therapy. O. Caffo [20] et al. presented data on the effectiveness of using this combination after progression that occurred against the background of the 1st line of docetaxel therapy. Docetaxel was administered on day 2 in combination with oral administration of estracite at a daily dose of 840 mg, divided into 3 doses, from the 1st to the 5th days of the cycle. Regression of the PSA level was recorded in 52% of cases. The median progression—free survival was 15, and the overall survival was 61 weeks. Thus, repeated administration of Taxotere in monotherapy, as well as the use of a combination of Taxotere with other drugs in the 2nd line of treatment, are effective in patients with progressive GRPJ. There is no standard approach in this difficult clinical situation yet. However, the data obtained in the studies are encouraging and allow us to hope for further improvement in the results of treatment of this difficult category of patients. Currently, research is actively underway to find drugs that are effective in the 2nd line after the use of docetaxel. O. Sartor et al. [21] presented the results of a phase III study on the use of a combination of cabazitaxel with prednisolone in patients with GRPJ who had previously received CT, the base drug of which was Taxotere (Tropic Trial). Cabazitaxel also belongs to the group of semi-synthetic taxanes, and in its chemical formula there are changes in two radicals compared to the docetaxel formula. Mechanism of action ONCOUROLOGY 1’201 In preclinical studies, the effectiveness of the drug against docetaxel-resistant tumor models has been proven. This study was conducted in 146 centers from 26 countries, including Russia. A total of 755 patients were included. Stratification was carried out according to the activity status of patients (0, 1 compared to 2 on the ECOG scale) and measurable and unmeasurable formations. Patients were randomized into 2 groups: in the 1st, cabazitaxel was treated at a dose of 25 mg/m2 once every 3 weeks in combination with prednisolone – 10 mg / day, in the 2nd, mitoxantrone was administered at a dose of 12 mg / m2 with the same interval in combination with prednisolone. The main purpose of the study was to assess overall survival, secondary were the analysis of disease-free survival, regression frequency and tolerability. The study included patients with measurable progressive diseases according to RECIST criteria, identified new foci or progression in PSA levels.

Results and conclusion. The characteristics of patients in terms of disease prevalence, demographic and other indicators were identical. According to the results of the analysis, in the group with the use of mitoxantrone, the median overall survival was 12.7, and in the treatment with cabazitaxel — 15.1 months (risk ratio 0.72, 95% CI 0.61–0.84). The differences were significant ($p < 0.0001$). The median progression-free survival was 2 times higher in the cabazitaxel group compared with that in patients treated with mitoxantrone and was 2.8 and 1.4 months, respectively ($p = 0.0002$). PSA and time-to-progression scores were also better in the cabazitaxel group. In the study of toxicity and tolerability, it was found that in the cabazitaxel group, the most common side effects of grade III–IV were febrile neutropenia (7.5% of cases) and diarrhea (6.2%).Thus, the use of cabazitaxel in this study was accompanied by an improvement in overall survival (compared with the results obtained with the use of mitoxantrone), a 28% reduction in the risk of death, as well as an increase in the median time to progression and response to PSA content. The data obtained indicate that cabazitaxel is a potentially new drug that can be used to treat patients with GRP after they undergo docetaxel therapy. Currently, cabazitaxel has already been included in the recommendations of the European Association of Urologists as a 2nd-line therapy drug used in patients with progression that developed after their 1st-line treatment with docetaxel [22]. To date, kabazitaxel has been registered so far only in the USA. In conclusion, it should be noted that the therapy of patients with GRP remains a difficult problem. A differentiated approach to the treatment of these patients makes it possible to make the right decisions taking into account their clinical condition, the kinetics of PSA levels and other indicators. The use of Taxotere in the 1st line of therapy is the most effective method of treatment and contributes to prolongation and improvement of the quality of life of patients. Repeated administration of Taxotere in a number of patients also allows to increase their life expectancy without a significant deterioration in its quality associated with the use of the drug. The development of new 1st-line therapy regimens based on Taxotera is the subject of an active search and is carried out in order to further improve the results of treatment. A study using cabazitaxel has demonstrated the effectiveness of using it as a promising 2nd-line drug in patients with GRPJ with progression that developed after docetaxel therapy, which provides new opportunities to improve treatment results. Hormone therapy is the standard of treatment for patients with prostate cancer, however, after a period of stabilization in most patients, the disease progresses and acquires a castration-resistant form. The management tactics of this group of patients is a complex problem of modern clinical oncourology. The possibilities of using surgical intervention and radiation therapy in a widespread malignant process are very limited, therefore, primary docetaxel-based chemotherapy is the leading treatment method. Unfortunately, the possibilities of using this method are also limited due to the fact that after 6-8 months, all patients develop a relapse of the disease. The results of numerous clinical trials show that the use of a combination of drugs with different mechanisms of action, as a rule, enhances the therapeutic effect.

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