Case report

Apalutamide in the treatment of a patient with non-metastatic castration-resistant prostate cancer

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ABSTRACT

The treatment of patients with prostate cancer, who do not qualify for the radical therapy is based on the use of surgical or pharmacological castration methods. The effectiveness of the so-called androgen deprivation tends to decrease over time. Even in the case of absence of distant metastases on imaging studies, the resistance for the hormonal castration may be developed. At this moment, the use of new generation androgen receptor inhibitors may reduce the risk of metastases or death. The paper presents a case report of a patient with prostate cancer without distant metastases who started therapy with apalutamide at the moment of developing resistance to the pharmacological castration.

Key words: prostate cancer, castration-resistant, androgen receptor inhibitor

INTRODUCTION

The growing prostate cancer morbidity is a major health problem worldwide. In most European countries, including Poland, it is the most frequent malignant cancer among men. The most important risk factor is the age. According to the World Health Organisation's estimates, in 2040 globally, the number of new cases in patients aged over 70 will double (710,000 cases in 2020 vs. 1.4 million in 2040) [1]. The choice of the treatment method depends on the baseline degree of advancement of the disease.

In patients not qualifying for the radical treatment, conservative management is applied, involving reducing androgen levels and the inhibition of the androgen receptor signalling pathway. The biological basis is the androgen-dependency of prostate cancer. Blocking androgen stimulation allows achieving the clinical response and slows down the growth process [2]. During hormonotherapy, however, there appear clones of proliferating cells irrespective of the maintained castrate testosterone levels [1]. Understanding and overcoming the mechanisms causing the resistance to androgen deprivation therapy (ADT) are the preconditions for the efficacy of further treatment of prostate cancer patients [3].

CASE STUDY

In August 2019, a patient aged 64 was referred to urological outpatient clinic due to the urinary retention symptoms and increased prostate-specific antigen (PSA) levels: 141 ng/mL. During the digital rectal examination (DRE), the following was observed: prostate hard, uneven, lateral grooves vanished. In the transrectal ultrasonography (TRUS): prostate with distorted zone structure, uneven echogenicity, protruding into the bladder area, areas of the decreased echo-structure infiltrate both trapezoid fields, seminal vesicles, and the bladder neck. The patient was qualified for core biopsy of the prostate. In September 2019, basing on the histopathologic examination, prostate cancer was diagnosed (adenocarcinoma Gls 4+5 and 5+5).

As a next step, the diagnostics was extended by the PET-18-F-FCH (18F-choline positron emission tomography) and magnetic resonance of the true pelvis. Both imaging scans confirmed the presence of expanding prostate infiltration lesion, bilaterally infiltrating the seminal vesicles as well as the bladder, with the metastases to the left external lymph nodes, diameter 22 mm. The baseline advancement level was assessed as cT4N1M0. On the diagnosis, the patient was in a good general condition (WHO 0), negating any cancer related pain. For many years, he had been under the care of diabetes outpatient clinic due to insulin-dependent diabetes mellitus. In September 2019, after obtaining the result of the histopathologic test, the hormonal therapy was started with the palliative intent. Initially, degarelix was administered for 3 months – GnRH (gonadotropin-releasing hormone) antagonist and at the next stage leuprorelin acetate – long-acting GnRH analogue. During the 12 months monotherapy with GnRH analogue PSA nadir totalled 6.4 ng/mL Starting from December 2020, due to the repeated increase in PSA levels, a decision was made to apply maximum androgen blockade (MAB). First, flutamide was introduced and, in July 2021, another antiandrogen - bicalutamide.

During the double hormonal therapy, the further increase in PSA level was observed in the consecutive months. In December 2021, the marker concentration totalled 22 ng/mL, while the testosterone level remained < 50 ng/dL. In January 2022, imaging scans were repeated. Scintigraphy and CT of the abdominal cavity and true pelvis did not confirm the presence of any lesion suspected of being metastatic. The treatment with bicalutamide was ended in early 2022, whereas at the time there were no other pharmacological options for nmCRPC (non-metastatic castration-resistant prostate cancer).

In March 2022, in line with the changes to the applicable drug programme [4], the patient was qualified for treatment with apalutamide – a new generation androgen receptor inhibitor (ARi). At the start of treatment, on 15 March 2022, PSA level was 48 ng/mL, whereas testosterone remained within the limits of castrate level < 50 ng/dL. PSA doubling time (PSADT) was < 10 months. The patient currently continues treatment with apalutamide. Control tests indicate gradual decrease of PSA levels (48 ng/mL in March 2022, 15 ng/mL in June 2022, 12 ng/mL in September 2022, 11.2 ng/mL in December 2022, 10.8 ng/mL in March 2023). The patient remains in a good general health condition and is professionally active. No adverse events have been observed during the treatment. The imaging scans (scintigraphy and CT of the chest, abdominal cavity, and true pelvis with contrast) repeated in September 2022 did not reveal any cancer metastases.

DISCUSSION

Prostate cancer is a hormone-dependent cancer. The application of surgical or pharmacological castration is the first line treatment in patients not qualifying for the radical treatment. ADT delays disease progression, reduces the risk of complications, and alleviates the cancer related symptoms [2]. With time, the efficacy of hormonal treatment decreases, and finally all pa-

tients develop resistance to ADT [2, 3]. The duration of cancer remission during hormonal therapy varies but, on average, it amounts to approximately 24 months [2]. Resistance to ADT is testified by increasing PSA levels at effective castration (testosterone level < 50 ng/dL or 1.7 nmol/L) [3].

In order to determine the diagnosis of castration-resistant prostate cancer (CRPC), three conditions determining the increase in PSA levels must be met [4]:

- documented three consecutive increases to PSA levels at intervals of at least one week
- two of them must be at least 50% higher than nadir
- nominal PSA level must be above 2 ng/mL.

Resistance to hormonal castration can also be determined in the absence of metastases in imaging scans (nmCRPC, non-metastatic castration-resistant prostate cancer) [3]. The procedure in nmCRPC depends on the PSA growth dynamics. Patients with high risk of metastases are considered to be the ones whose PSADT is ≤ 10 months [5]. So far, three ARi have been registered in the treatment of nmCRPC in high-risk patients in combination with ADT: apalutamide, darolutamide, and enzalutamide. For each of them, in combination with ADT, statistically significant extension of metastasis-free survival vs. ADT + placebo was documented [6–8].

In the case of the analysed patient, the treatment was started with GnRH antagonist. The main cause was the neoplastic infiltration reaching the neck of the bladder, and the urinary retention symptoms. Degarelix immediately inhibits gonadotropin hormones by the pituitary, which consequently reduces the risk of flare-up effect [3]. Continuation of hormonal therapy was first based on the application of long-acting GnRH analogue, and then MAB. In view of current guidelines, the application of double hormonal blockade is a controversial procedure, which principally affects the time to the biochemical progression. There are no randomized data indicating benefits to overall survival vs. administration of GnRH agonist alone [5]. Nevertheless, at the time, there were no other pharmacotherapy options at the nmCRPC stage.

The dynamics of PSA level increase and PSADT < 10 months qualified the patient to the nmCRPC group with the high risk of metastases. In line with the changes to the drug programme introduced in March 2022, the patient was qualified for treatment with ARi [4]. Apalutamide has chemical and pharmacological properties similar to enzalutamide, but is characterised with longer half-life, greater affinity to androgen receptor, and poorer permeability to the central nervous system [3]. In Phase III trial, in the group of high-risk nmCRPC patients, the administration of the drug (240 mg/24 h) was related to statistically significant extension of metastasis-free survival (MFS) vs. placebo (HR = 0.28; 40.5 months vs 16.2 months) [6]. After median observation time of 52 months, the improvement of median overall survival (mOS) in the group receiving apalutamide vs. placebo amounted to 73.9 months vs 59.9 months (HR = 0.78) [9]. As regards the secondary endpoints, the group receiving apalutamide recorded significantly longer: metastasis-free survival time (HR = 0.27), time to progression (HR = 0.29), and time to symptomatic progression (HR = 0.45) [6]. Adverse events causing discontinuation of treatment occurred in 10.6% patients, and in 7.0% in the placebo group. Grade 3 and 4 adverse events were observed in 45.1% of patients in the group receiving apalutamide, and in 34.2% in the placebo group. Most frequent adverse events included fatigue (30.4%), hypertension (24.8%), rash (23.8%), and diarrhoea (20.3%) [6].

CONCLUSION

The analysed case documents the favourable therapeutic effect after administration of apalutamide in a patient with nmCRPC. The application of the new generation antiandrogen is a valuable therapeutic option which contributes to reducing the risk of metastases and death.

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