Case study

Apalutamide in the treatment of non--metastatic castration-resistant prostate cancer in an elderly patient with multiple comorbidities

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ABSTRACT

Prostate cancer has been the most common malignant tumor in men in Poland since 2016 and is the second cause of death in this group of patients. The basic method of treatment in patients with advanced prostate cancer is androgen deprivation therapy, however, over time, the tumor evolves into a castration-resistant form, which poses a significant threat to the patient's life. This article presents a case of an elderly patient with internal diseases, who in the castration-resistant stage, was treated with a new generation androgen receptor blocker – apalutamide – in the first line of systemic treatment.

Key words: non-metastatic castration-resistant prostatic cancer, androgen receptor, apalutamide

INTRODUCTION

Prostate cancer is the most frequent urogenital cancer in men. In 2020, the number of new occurrences totalled 14,244 cases. Prostate cancer is characterised with the highest morbidity dynamics and a growing tendency of mortality prevailing since 2004. The data published in 2022 indicate that it currently ranks as number one in malignant cancer morbidity in men in Poland (19.5% cases) and ranks second as the cause of death in this group (10.8% deaths) [1]. Treatment of patients with advanced prostate cancer involves pharmacological or surgical castration – androgen deprivation therapy (ADT) [2] but, in time, most of them develop ADT resistance [3], manifested with increase in prostate-specific antigen (PSA) levels and shortening of prostate-specific antigen doubling time (PSADT) [4]. Patients who, despite ADT, record increase prostate-specific antigen levels in the absence of metastases in imaging scans are diagnosed with non-metastatic castration-resistant prostatic cancer (nmCRPC) [2].

Patients whose PSADT totals ≤ 10 months are classified into high-risk group in the aspect of metastases occurrence and death due to nmCRPC [5, 6]. Therefore, supreme therapeutic objectives include: metastasis prevention, maintenance of the quality of life, and extension of overall survival [5, 7].

The drug currently registered for nmCRPC treatment is apalutamide [8, 9]. It is a selective and irreversible inhibitor of androgen receptor (AR) which binds directly to the AR ligand binding domain; in this way, it prevents translocation of the AR complex to the cell nucleus, which inhibits its binding with DNA and blocks the AR-initiated transcription [10]. Hormonotherapy with apalutamide is a highly effective treatment in the aspect of extending the progression-free survival (PFS), time to metastasis (TTM), and overall survival (OS) with simultaneous good tolerance [11].

This article is a case study of a patient treated for 24 years due to prostate cancer, currently with apalutamide.

CASE STUDY

In January 1999, patient aged 63 with hypertension reported to the urological outpatients' in Szczecin due to PSA level elevated to 10 ng/mL. He was admitted to the Urological Department of the Pomeranian Medical University (PMU) where, on 15 February 1999, he underwent transrectal ultrasound (TRUS) and core biopsy, and was diagnosed with advanced prostate cancer. Based on computed tomography (CT) imaging and bone scintigraphy, metastases were eliminated, and the disease progression was estimated as cT1N0M0. During the hospitalization, the patient was proposed surgical treatment – radical prostatectomy, but the patient refused to give his consent to the procedure. Therefore, after the consultation at the Radiotherapy Department at PMU in Szczecin, the patient was qualified for external beam radiation therapy (EBRT). In the period from March to April 1999, the patient received 66 Gy in 33 fractions in the prostate and seminal vesicles area. The patient remained under the care of urological outpatients' where he received hormonal treatment, first in the form of maximum androgen blockade (MAB) with luteinising hormone-releasing hormone (LHRH) analogue in combination with antiandrogen drug, while later with the LHRH analogue in monotherapy; as a result, PSA levels dropped to < 0.2 ng/mL.

In July 2021, the first increase to PSA level was recorded: 7.71 ng/mL. The patient arrived at the Oncological Outpatients of West Pomeranian Oncology Center in Szczecin in October 2021. The patient was referred by urologist in charge due to PSA levels increasing from May 2021 for possible qualification for systemic treatment (tab. 1).

Table 1. Prostate-specific antigen (PSA) levels during the treatment at the urological outpatients'.

Date	Serum PSA level (ng/dL)
1.03.2021	1.23
31.05.2021	4.79
29.07.2021	7.71
27.08.2021	9.06
4.11.2021	15.77
4.01.2022	19.15

The consulting radiotherapist recommended positron emission tomography – computed tomography (PET-CT) fluorine-18 (18F)-labelled choline. Test results include diagnosis of local recurrence, but no metastases were revealed. On 4. November 2021, the patient brought the PET-CT result to the consultation with a clinical oncologist, who again titrated PSA (result: 15.77 ng/mL) and testosterone level (< 50 ng/dL). During the visit, despite the advanced age (85), the patient remained in a very good general condition (ECOG/WHO 0), and only complained about being week (score 1 acc. to CTCAE) and periodical hot flushes (score 1 acc. to CTCAE), negated any pain in bones, and did not take any pain killers. He remained under cardiological care due to hypertension and arrythmia, as stated in the interview. The diagnosis was nmCRPC. The patient did not require chemotherapy: he had no clinical symptoms of the disease, the tumour weight remained low, and there was no risk of visceral crisis. Due to absence of metastases in remote organs, the patient did not meet the inclusion criteria for the treatment programme of the Polish

National Health Fund before chemotherapy. Due to dynamic growth in the marker levels and PSADT totalling 2.7 months, the decision was made to administer treatment with selective AR inhibitor. On 16 February 2022, treatment with apalutamide was started within the extended access to the drug, while keeping hormonal castration. Baseline PSA level at the onset of treatment totalled 19.74 ng/mL. On 16 March 2022, the patient was qualified for treatment continuation within the framework of treatment programme of the Polish National Health Fund, and continues to administer apalutamide until present. Control imaging scans performed after 6 months of treatment, the disease was stable (SD, stable disease), and PSA levels systematically decreased, achieving the lowest value so far: 2.63 ng/mL (nadir) on 2 November 2022 (tab. 2).

Table 2. Prostate-specific antigen (PSA) levels during the treatment with apalutamide.

Date	Serum PSA level (ng/dL)
16.02.2022	19.74
13.04.2022	4.89
3.08.2022	3.03
2.11.2022	2.63

The patient continues treatment. Until 28 December 2022, he received 11 cycles of apalutamide treatment in due doses. He remains in a very good general condition (ECOG/WHO 0), does not feel cancer symptoms, and does not report any adverse events.

DISCUSSION

The above case study refers to diagnosis of prostate cancer in a middle-aged man, and is an example of long-term survival and clinical benefit for the patient owing to the sequential systemic treatment. Due to intermediate prognostic factors and the expected slow disease progression, as well as the rather young age of the patient upon disease occurrence and expected natural survival of > 10 years, radical prostatectomy was proposed. The patient did not agree to the procedure because he did not accept the risk of related complications. Due to absence of the consent to the procedure, the patient was qualified for tele-radiotherapy which, according to the guidelines, is an equivalent alternative for surgical treatment in patients with the disease at the local stage [12]. During the irradiation of the prostate and after its completion, the patient remained under strict urological control, combined with ADT, first as MAB, and then with LHRH analogue in monotherapy. This procedure is questionable because it results with extension of progression-free survival and OS extension as compared to delayed treatment exclusively in patients with a high risk of metastasis, to which group the patient did not belong upon diagnosis [13]. After radical treatment, hormonotherapy was intermittent (IAB, intermittent androgen blockade) principally with the objective of improving the patient's quality of life without affecting survival rate [14]. Monotherapy with LHRH analogue lasted 20 years and, according to the above description, was well tolerated, while typical adverse events were not inconvenient enough for the patient to decide to discontinue treatment.

After 20 years of ADT, the patient was diagnosed with nmCRPC, which enforced treatment modification. High dynamics of PSA increase, with PSADT totalling 2.7 months, indicated that the patient belonged to the group with high risk of metastases [5]. Due to advanced age and cardiological condition of the patient, long history of the disease, absence of metastases, and no risk of visceral crisis, a decision was made to continue hormonotherapy and supplement ADT with androgen receptor blocker: apalutamide. The above case study shows that the application of the treatment also in a group of elderly patients with internal diseases is an effective and safe therapeutic option [11]. It allows avoiding chemotherapy, and thus gives the opportunity of avoiding many complications related to cytostatic toxicity. During the treatment with apalutamide, the patient remains in very good general health, does not experience any clinical symptoms of the disease, or any adverse effects, which allows him to continue his active life style. Clinical benefit from the treatment includes PFS currently amounting to 12 months.

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