Case report

Apalutamide as a therapeutic option in case of local failure in the nmCRPC

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ABSTRACT

Apalutamide is a non-steroidal selective androgen receptor inhibitor approved for the treatment of high-risk non-metastatic castration-resistant prostate cancer and metastatic hormone-sensitive prostate cancer. The paper describes a case of a patient diagnosed with prostate cancer with a long-term course of the disease. The patient was diagnosed with a non-metastatic castration-resistant stage 18 years after primary treatment. Systemic treatment with apalutamide was recommended. Initially, the treatment was carried out as part of the extended access to apalutamide program and from March 2022 as part of the B.56 drug program. The study presents the effectiveness and safety of the therapy in a 12-month follow-up period and discusses controversial aspects of the patient's previous treatments.

Key words: prostate cancer, castration resistance, apalutamide

INTRODUCTION

Prostate cancer is the most frequent cancer in men in Poland (morbidity: 20.6%). It ranks second after the lung cancer in the aspect of mortality (10.3%). The cancer is characterised with the highest dynamics of morbidity growth. Mortality remained at a stable level in the early 21st century, but has shown a growth tendency since 2004 [1]. Prostate cancer treatment efficacy is relatively high, but it still remains an important reason for premature mortality in adult men.

Prostate cancer treatment methods depend on disease progression upon diagnosis. In the early stage, surgical treatment is applied, various radiotherapy techniques (including stereotactic radiotherapy and brachytherapy) and hormonotherapy (HT) based on gonadotropin-releasing hormone (GnRH) analogues or antagonists. In the case of metastases or castrate-resistant prostate cancer (CRPC) stage, apart from the aforementioned radiotherapy and hormonotherapy, applied treatments include chemotherapy based on docetaxel or cabazitaxel, hormonotherapy using state-of-the-art antiandrogens, and 223Ra. European Association of Urology (EAU) recommends that patients with the diagnosis of M0 CRPC with PSA doubling time (PSADT) < 10 months should be offered treatment based on apalutamide, darolutamide, or enzalutamide [2].

The population diagnosed with prostate cancer comprises of elderly patients, often with concomitant diseases. Safety profile constitutes a major factor affecting the choice of treatment. Hormonotherapy based on second generation antiandrogens is characterised with high efficacy in the aspect of extending the progression-free survival and overall survival, as well as very good tolerance.

CASE STUDY

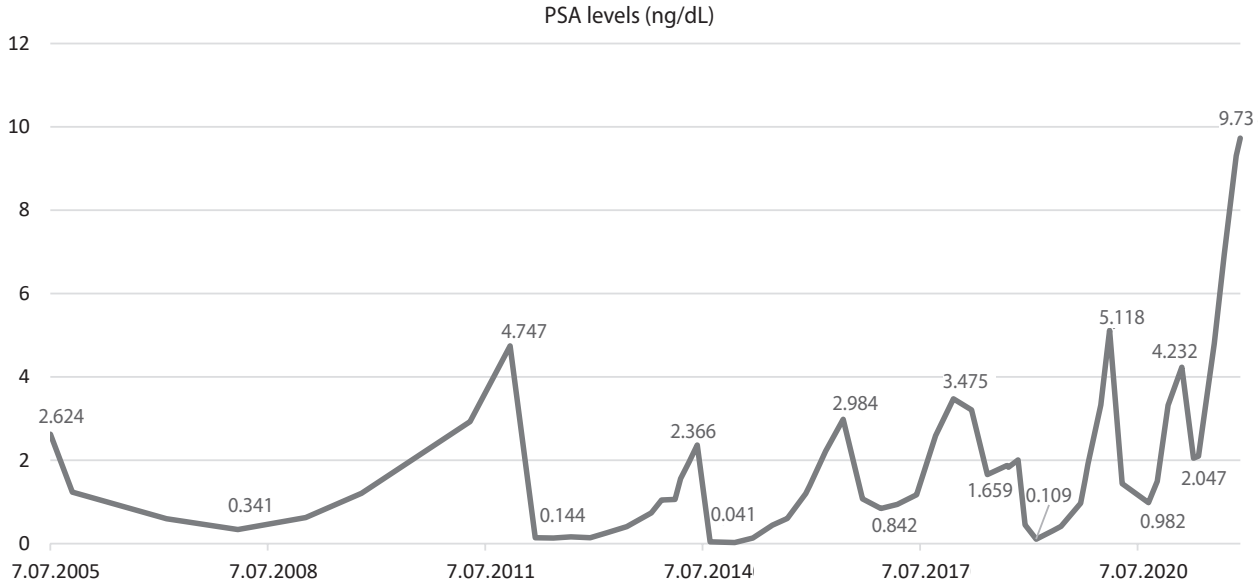
Patient aged 60 began prostate cancer diagnostics in July 2004 due to elevated PSA (prostate-specific antigen) levels totalling 8.3 ng/mL. Core biopsy led to histopathologic diagnosis: adenocarcinoma Gleason 3+3. The biopsy resulted in acute prostatitis and cystitis, involving the need for temporary catheterization into the bladder. Imaging scans did not show any metastases to regional lymph nodes or any metastases. Per rectum examination led to diagnosis of local progression of cT2b. The patient was classified in the group of medium risk of biochemical recurrence [2], and a decision was made to apply radiotherapy according to the regime applicable at our centre at the time. As the first phase of treatment on 20 November 2004, boost was conducted using high-dose-rate brachytherapy (HDR-BT) using 192Ir as iridium source; total dose administered: 10 Gy in a single fraction. Next, in the period between 6 December 2004 and 12 January 2005, external beam radiotherapy (EBRT) was performed with fraction dose of 2 Gy to total dose of 44 Gy in the regional lymph node area, and fraction dose of 2 Gy to total dose of 54 Gy in the prostate area. No hormonal treatment was applied at the time.

After completion of radiotherapy, the patient remained under permanent control, with PSA level titrated every 3–6 months. Due to PSA level increase meeting the Phoenix criteria for biochemical recurrence (PSA nadir + 2 ng/mL) [3] in November 2011, magnetic resonance imaging (MRI) was performed with the image corresponding to local recurrence within the right-side of the prostate. The patient was qualified for systemic treatment based on goserelin, which started in December 2011. Starting from May 2013, a slow increase in PSA level was observed despite the applied hormonotherapy (fig. 1). Due to ineffectiveness of pharmacology at the time, a decision was made to implement local treatment: the patient was proposed emergency radiotherapy or radical prostatectomy. The patient did not give consent to surgical treatment. Therefore, he was qualified for life-saving treatment using stereotactic body radiation therapy (SBRT).

Between 10 and 20 June 2014, SBRT was performed using CyberKnife® X 6 MV photons on the recurrence area in the right lobe of the prostate with margin with fraction dose of 6 Gy to total dose of 30 Gy. One year after the emergency radiotherapy, despite continuation of treatment with GnRH analogue, PSA levels started increasing again and, in June 2016, achieved the value meeting the Phoenix criteria for biochemical recurrence. Due to absence of other therapeutic options, goserelin was supplemented with bicalutamide. Nevertheless, after just 12 months of applying maximal androgen blockade (MAB), PSA increase was observed again. On 30 November 2017, prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) was performed to monitor any lesions suspected to cause local recurrence or metastases. PET scan provided the image of recurrence of underlying disease in the prostate pulp on the right side, without metabolic properties of remote metastases. Due to absence of other treatment options, existing hormonotherapy was continued. PSA levels began to decrease, probably in relation to the introduction of treatment with dutasteride.

At another biochemical progression, MRI of the prostate was performed (27.09.2018), which described disease progression: cancer infiltration in the central part and peripheral zone of the right prostate lobe, passing onto the bladder wall on the right

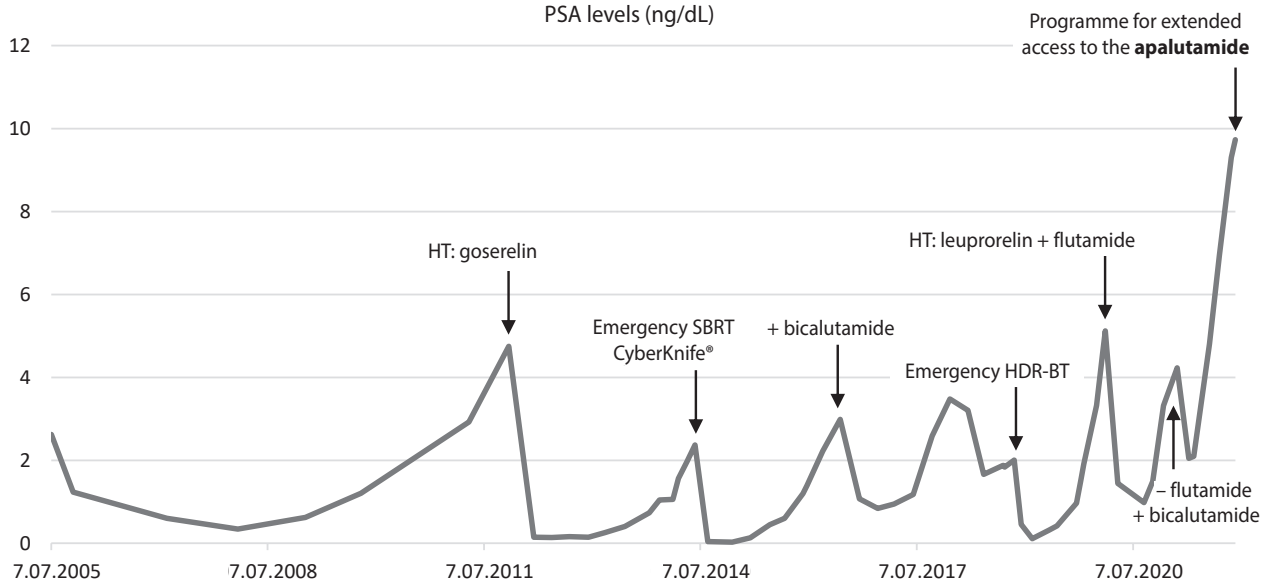
Figure 1. PSA level kinetics in the period 2005–2021.



side and onto the right seminal vesicle. On 15.10.2018, biopsy of the prostate was performed, which confirmed recurrence within the area of right prostate lobe and the right seminal vesicle. Gleason score was assessed as 4+5. The patient was qualified for local treatment using brachytherapy. HDR 192Ir brachytherapy was performed on 20.11.2018 in subarachnoid anaesthesia, administering the dose of 19 Gy onto the recurrence area in the right prostate lobe and the right seminal vesicle. Quick drop of PSA level after radiotherapy caused the decision to have a break in hormonotherapy applied for 7 years already (fig. 1, 2).

Another biochemical progression occurred after 8 months, with PSA of 5.118 ng/ml in February 2020. MRI from 22.10.2019 revealed partial regression of infiltration lesions at the right-side of the prostate. The infiltration in the posterior wall, on the right side of the bladder, was similar as in the previous scan. The new findings, however, included unclear area at the base of the prostate on the left side, and pathological area, suspected to be inflammatory or cancer infiltration at the upper wall of the bladder on the left, which had not been visible earlier. PET PSMA of 26.02.2020 illustrated local recurrence of cancer in both pros-

Figure 2. Regime of applied therapies at the PSA level diagram in the period 2005–2021.



tate lobes, without metabolic features of metastases. In March 2020, treatment was started using MAB (leuprorelin + flutamide), achieving quick response in the form of PSA levels reduced to 0.982 ng/mL in 5 months. At another biochemical progression and with exclusion of metastases, due to prior treatment and the application of maximum androgen blockade, and in the absence of other options, a decision was made to replace flutamide with bicalutamide. Short stabilisation of PSA levels was achieved, after which another, quick biochemical progression was observed (fig. 1, 2). PET PSMA performed in September 2021 revealed a single location of the underlying disease in the prostate pulp and at the posterior wall of the bladder, with the features of partial metabolic regression vs. the scan from 26.02.2020.

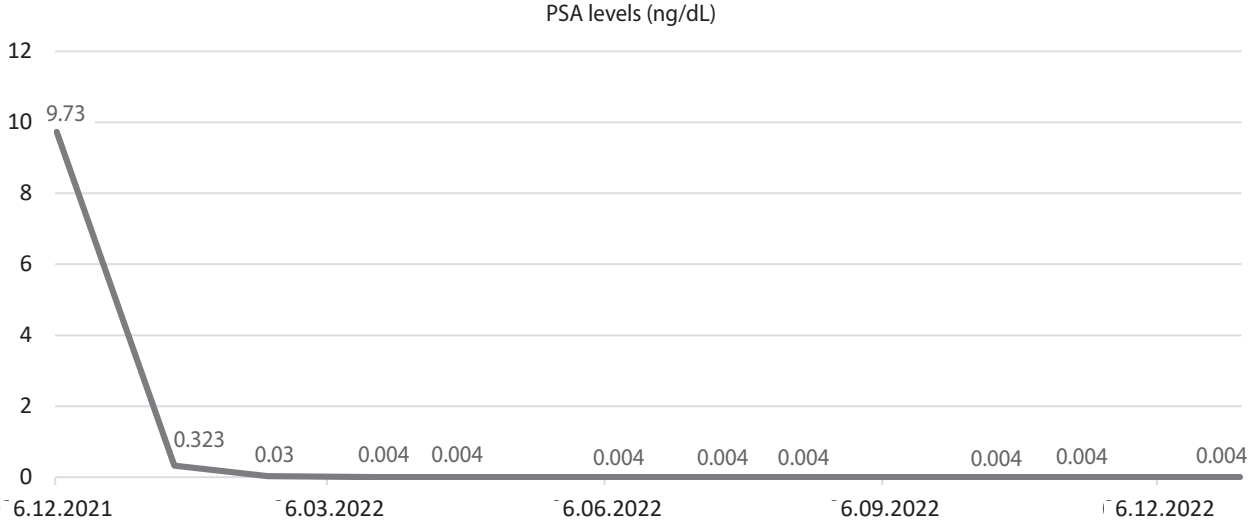
Prior treatment had proved ineffective. Several radiation cycles in the pelvic area closed the path to another local treatment using both radiotherapy and surgery. Absence of metastases in imaging scans excluded the option for a systemic treatment other than the already applied MAB. In December 2021, PSA level reached 9.73 ng/mL, with testosterone level of 0.2 ng/mL; PSADT totalled 8.3 months. CT of the neck, chest, abdominal cavity and pelvis, as well as bone scintigraphy did not reveal any remote and regional metastases. The diagnosis was the stage of non-metastatic castration-resistant prostate cancer (nmCRPC, or M0 CRPC).

According to EAU guidelines, patients diagnosed with M0 CRPC and with PSADT < 10 months should be offered treatment based on apalutamide, darolutamide, or enzalutamide [2]. Owing to the programme for extended access to the drug, the patient began treatment with apalutamide on 14 December 20201. In turn, starting from March 2022, after update of B.56 drug programme, the treatment was continued within its framework.

After the introduction of apalutamide, quick decrease in PSA levels was achieved, amounting to 0.323 ng/mL in mid-January 2022 (fig. 3). In March 2022, indeterminable level was achieved (< 0.004 ng/mL), which was maintained until November 2022. After almost 2 weeks of treatment, itching rash appeared, which disappeared within a few days after administration of antihistamine drugs. Control CT performed on 28.02.2022 revealed local recurrence with infiltration onto the posterior-right wall of the bladder, with the size similar to the one recorded in the previous scan, acc. to RECIST 1.1 – stagnation. Bone scintigraphy of 8 June 2022 excluded metastases to the bones.

In May 2022, urinary retention occurred. At the urological outpatients', the patient was catheterized into the bladder and, following multiple expansion of the urethra using plastic expanders, experienced subsequent bleeding from the urethra. Starting from June 2022, the patient reported intensifying symptoms: diarrhoeas, pain in the lower abdomen and perineal area. At the end of June, due to the impossibility of maintaining urethra patency without a catheter, due to the past treatment and post-inflammatory exacerbation of chronic pain, suprapubic cystostomy was recommended. Early in August, elevated body temperature occurred, with exacerbated pelvic pain that radiated into the groin, hip, and legs, causing problems with mobility. Therefore, a break in apalutamide administration was recommended. Under the control of urological outpatients', antibiotic treatment was introduced, and control laboratory tests and scans were requested.

Figure 3. PSA level kinetics during the treatment with apalutamide.



MRI from 18.08.2022 described the areas of pathologic enhancement with the properties of obstructed diffusion around the bladder neck and the urethra. Similar lesions were observed in the muscle area, at the pubic symphysis, more intense on the left side. The image supplemented with clinical data indicated massive inflammatory lesions with developed abscesses in the above locations. Urine culture indicated Pseudomonas aeruginosa CP(-) (>1,000,000 CFU/mL) and Enterococcus faecalis HLAR(-) (>1,000,000 CFU/mL).

Targeted antibiotic therapy was introduced according to the result of urine culture with antibiogram (fig. 4). Significant improvement was achieved, with alleviated pain, fever and gastrointestinal symptoms. The symptoms occurring since June were most probably related to the exacerbation of post-radiation inflammatory lesions in the pelvic area as a result of urological interventions.

Figure 4. Result of urine culture test of 25.08.2022.

	Antibiogram			
	1		2	
Antibiotic	**Result**	**MIC**	**Result**	**MIC**
Nitrofurantoin			S	32
Amikacin	WZE	16		
Ampicillin			S	2
Ceftazidime	WZE	8		
Ciprofloxacin	WZE	0,5	S	1
Cefepime	WZE	8		
Gentamicin	R			
Gent. Synergy			S	500
Levofloxacin	WZE	2	S	1
Pip/Tazo	WZE	16		
Strep. Synergy			S	1000

S – sensitive, WZL – sensitive, increased exposure, R – resistant, MIC (mg/L) zone (mm).
Interpretation of drug sensitivity according to EUCAST recommendations.

DISCUSSION

The presented medical history is abundant with controversies. The discussion should begin with the first radiotherapy regime used at the turn of 2004 and 2005. EBRT treatment with fraction dose of 2 Gy to 44 Gy in the area of pelvic lymph nodes and up to total dose of 54 Gy in the prostate area with the HDR-BT boost with fraction dose of 10 Gy in 1 fraction is characterized with insufficient efficacy and has not been applied for many years. While adopting the value of $\alpha/\beta = 3$ Gy for prostate cancer, biologically effective dose (BED) in the applied regime equalled 133.3 Gy. Retrospective analysis of prostate cancer treatment results in our centre showed that BED higher than 135 Gy involves a significantly lower risk of biochemical recurrence [4]. The presented case confirms ineffectiveness of the applied radiation regime both in the aspect of biochemical and local control.

Further doubts might be raised by the application of emergency SBRT. The choice of such a treatment was principally caused by the patient's refusal of surgical treatment. The available studies suggest high efficacy and low toxicity of emergency SBRT [5–8], but the number of patients treated this way is rather low, whereas the observation time is too short to consider this a standard procedure. In the analysed case, radiation involved exclusively the local recurrence area with a margin, without covering the entire prostate. This was aimed at reducing toxicity of another radiotherapy in the pelvic area. Literature data regarding such therapies are very restricted, and refer to very small groups of patients with short observation time following treatment. It is suggested that such treatment is well tolerated and is characterised with satisfactory efficacy. There are, however, no clear selection criteria for the treatment [9, 10].

The decision to apply radiotherapy for the third time seems the most controversial. From the time perspective, one can suspect that emergency surgical treatment would probably be more effective, but also bearing a high risk of complications. In 2018, after two radiation cycles of the pelvis, the patient was not qualified for surgical treatment. Absence of other therapeutic options and the risk of uncontrolled local disease progression contributed to this bold treatment attempt. There are no data on efficacy and safety of repeated emergency treatment using ionising radiation. The regime applied involved administration of total dose of 19 Gy in a single fraction, considered to be safe and effective in both emergency and primary treatment. Investigators also suggested efficacy of such dosage in focal therapy [11–13]. After a longer observation period, however, it proved significantly less effective than regimes involving several doses, and currently it is considered unjustified [14, 15].

According to EAU guidelines, in the case of biochemical recurrence following radiotherapy in patients whose general condition allows their qualification for emergency treatment, PSMA PET-CT should be performed (possibly PET-CT imaging with choline or fluciclovine). According to these guidelines, emergency treatment should be offered to a highly selected group of patients with local recurrence confirmed with core biopsy within the framework of clinical trials or a prospective cohort study in centres with considerable experience.

Toxicity of the treatment was rather low for many years, in particular considering triple radiation of the prostate using hy-

po-fraction regimes. Still before qualification for primary treatment, the patient was recorded for urinary retention in the bladder that required catheterization. After radiotherapy, these ailments discontinued. Intensification of urinary symptoms occurred in February 2018 with haematuria, micturition disorders of bladder outlet obstruction type, and recurring urinary infections accompanied with dysuria and polyuria. Empiric antibiotic therapy was applied with good effect. In June 2018, it was necessary to perform the bilateral bladder neck incision procedure. After the procedure, moderately intensified incontinence was observed, nycturia 4–5 times. Dutasteride and mirabegron were administered, achieving improvement. One year following treatment with emergency brachytherapy, weakened urine stream was observed, nycturia 4 times, and periodically burning sensation in the urethra at the end of micturition, and urgent pressure onto the bladder. In October 2019, it was necessary to catheterize the patient to keep urethral patency, with occurrence of pelvic pain and haematuria. Recurring urinary infections that responded well to targeted antibiotic therapy according to the urinary culture result with antibiogram. In October 2020, catheter was removed due to observed strong tendencies to overgrowth in the prostate section of the urethra, and decision on its expansion was made, achieving clear urine outflow. Due to incontinence, external catheter was installed for permanent. The most intensive symptoms occurred in mid-2022 (as discussed in the "Case Study" section).

In relation to diagnosis of stage nmCRPC, owing to the programme of extended access to the drug, the patient was introduced to treatment compatible with international guidelines [2, 16]. The efficacy of apalutamide in the treatment of patients with aforementioned diagnosis was proved in the SPARTAN study. The application of apalutamide combined with androgen deprivation therapy (ADT) in nmCRPC patients was related to extension of metastasis-free survival and time to progression of symptoms. The treatment was very well tolerated [17]. Further analyses also confirmed extension of time until second progression, extension of overall survival, and reduced risk of death by 25% [18, 19].

The analysed case of a patient with long-term prostate cancer confirms the efficacy and safety of apalutamide in the treatment of M0 CRPC stage during a short observation of 12 months. Apalutamide-based treatment is effective, well tolerated, and allows for control of the disease progression. The patient recorded just one adverse event which can be related to the treatment. This was a skin rash that disappeared quickly after application of symptomatic treatment.

CONCLUSION

Recently, there has been a breakthrough in the treatment of castration-resistant prostate cancer, not only in the metastatic stage, but also in patients without metastases. Nevertheless, the disease remains uncurable. Results of prospective clinical trials indicate efficacy of several drugs administration of which statistically significantly extends overall survival and time to disease progression with acceptable toxicity profile in patients at the stage of non-metastatic castration-resistant prostate cancer [17, 20, 21]. Changes to the regulations of B.56 drug programme introduced in March 2022 allowed treatment of nmCRPC patients using preparations registered for the indication.

Despite the fact that the number of effective therapeutic options in patients diagnosed with CRPC increased, there are still no direct comparisons of efficacy and safety of available treatment methods. Therapeutic decisions must be made on case-by-case basis. It seems that in asymptomatic patients in good general condition diagnosed with M0 CRPC, the application of state-of-the-art antiandrogens is a valuable treatment method that should be considered as first-line therapy.

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