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REVIEW ARTICLE

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Management of patients with metastatic castration-resistant prostate cancer — first-line treatment options according to the Polish National Health Found therapeutic program

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ABSTRACT

Prostate cancer is one of the most common malignancies among men worldwide. According to ESMO recommendations, systemic treatment of castrate-resistant prostate cancer (CRPC) patients includes hormonal treatment, radionuclides, and immunotherapy, and the choice of appropriate method depends, among others, on clinical symptoms of disease and possible presence of distant metastases. Polish recommendations regarding systemic treatment of CRPC are different, mainly due to the distinct reimbursement conditions for individual drugs. The purpose of the subsequent two publications is to present the options of systemic treatment for CRPC patients within the Polish National Health Fund drug program. The first of the articles presents first-line treatment.

Key words: prostate cancer, castration-resistant prostate cancer, systemic treatment, first-line setting

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Introduction

The prostate cancer is recognised as one of the most frequent cancers in men throughout the World. Its incidence is dynamically increasing while its mortality remains constant. It is the second most frequent solid tumour in Poland. In 2015 it constituted 17% of all cancers in men [1–3]. There were 14,200 new cases and over 4800 deaths in the same period of time in Poland (standardised morbidity rate and standardised mortality rate for prostate cancer of 43.83/100,000 and 13.39/100,000 per year, respectively) [2].

According to ESMO recommendations, the systemic treatment of castration-resistant prostate cancer (CRPC) consists of chemotherapy (docetaxel, cabazitaxel), novel hormonotherapy (abiraterone acetate and enzalutamide), radionuclides (^{223}Ra, alpharadin), and immunotherapy [autologous vaccine derived from dendritic cells modified *ex vivo* (Sipuleucel-T)]. The treatment choice should depend on the potential presence and intensity of symptoms related to cancer and/or the potential presence of distant metastatses [4, 5].

The recommendations for systemic treatment of CRPC in operation in Poland differ slightly from those recognised by the ESMO. In general the differences reflect the various terms of reimbursement for specific agents [1, 4–7]. The conditions for use of specific treatment modalities were defined in the announcement of Polish Ministry of Health from October 25th 2017 referring to the list of reimbursed drugs, food products, and means of special use and medical products (Dz. Urz. Min. Zdr. 2017.105, zał. B.56) [8].

The aim of the two subsequent publications is to describe options for first- and second-line systemic treatment for men with castration-resistant prostate cancer.

Systemic treatment in the first line

The initial treatment of prostate cancer includes surgery, radiotherapy, or systemic treatment. A detailed description of the aforementioned treatment modalities exceeds the scope of this publication.

The systemic treatment is mainly based on hormonal therapy with the aim to decrease serum concentration of testosterone to castration levels [testosterone concentration < 50 ng/dl (< 1.7 nmol/l)] [9, 10]. It is termed as pharmacological castration or androgen deprivation therapy (ADT). Such a strategy enables the control of the cancer in the majority (> 90%) of men with advanced prostate cancer. However, this modality should be considered as an alternative to surgical castration. Regardless of the method the castration was achieved in a majority of patients ultimately the resistance of cancer to castration is developed. Median time to development of CRPC is 18–24 months [10].

At this phase of the disease one of the first-line treatment options that has been available in Poland since November 2017 is abiraterone acetate. Abiraterone acetate is a selective inhibitor of P450 c17 (CYP17) cytochrome, the enzyme that is crucial for androgen synthesis in testis, adrenal glands, and, what is very important from the perspective of pathogenesis of CRPC, in tumour cells of prostate cancer. Abiraterone acetate decreases serum concentration of testosterone more effectively when compared to analogues or antagonists of luteinising hormone releasing hormone (LHRH). However, the decrease in the production of glucocorticosteroids during the use of the drug should be addressed. A secondary high concentration of adrenocorticotropic hormone (ACTH) occurs, which subsequently leads to increased synthesis of mineralocorticoids responsible for typical adverse events of abiraterone. These are: liquid retention with formation of peripheral oedema, hypertension, and hypokalaemia. The concomitant administration of prednisone addressed in the therapeutic program is the way to prevent the occurrence of the aforementioned side effects [5, 8].

The activity of abiraterone acetate in chemotherapy-naive CRPC patients has been assessed in the COU-AA-302 randomised prospective clinical trial. A total of 1088 men enrolled to the study received abiraterone acetate with prednisone or matching placebo. The observations in the abiraterone arm were as follows:

— improvement of median radiographic progression-free survival (rPFS) 16.5 *vs.* 8.3 months; hazard ratio (HR) 0.53; 95% CI (confidence interval): 0.45–0.62;
— reduced risk of deterioration of performance status (by 18%), reduced risk of deterioration in quality of life (by 22%), and risk of pain requiring opioids use (by 32%);
— improvement of median time to introduction of chemotherapy for CRPC (from 16.8 to 26.5 months);
— improved proportion of patients with biochemical response (62% *vs.* 24%) and radiographic response (36% *vs.* 16%);
— improved median overall survival (OS) (34.7 *vs.* 30.3 months; HR = 0.81; 95% CI: 0.70–0.93);
— defined and acceptable toxicity profile.

According to the Summary of Product Characteristics, abiraterone acetate with prednisone or prednisolone is indicated in the treatment of metastatic castration-resistant prostate cancer patients who failed to benefit from ADT, in whom chemotherapy is not yet clinically indicated, and who are asymptomatic or mildly symptomatic [11].

However, according to the terms of the NFZ therapeutic program, abiraterone is indicated in chemo-naive patients with castration-resistant prostate cancer [8, 12]. The drug should be used as described in the currently operational Summary of Product Characteristics for abiraterone: recommended daily dose of 1000 mg [four tablets of 250 mg or two tablets of 500 mg the dose is available since the beginning of this year) taken once a day] with low dose of prednisone or prednisolone (recommended daily dose of 10 mg). In patients who did not undergo the orchiectomy androgen suppression with LHRH agonists should be maintained during the abiraterone treatment. Dose modifications are allowed in cases and ranges described in the Summary of Product Characteristics for abiraterone. The treatment is conducted until the physician decides to withdraw the patient according to a letter of abiraterone therapeutic program defining the withdrawal criteria.

The inclusion/exclusion criteria of the abiraterone acetate therapeutic program and test list required before and during the treatment are presented in Table 1.

Summary

Currently abiraterone acetate in metastatic prostate cancer is generally used in the phase of resistance to castration. The drug can be administered either before or after chemotherapy. Such a possibility to use abiraterone in diversified strategy indicates the need to define the specific inclusion criteria for various stages of systemic treatment and different phenotypes of prostate cancer. Patients who probably benefit the most from treatment with abiraterone acetate lack of organ involvement, have no symptoms related to underlying disease or who are mildly symptomatic and men in good performance status (0–1 according to ECOG criteria) [5].

It is important that the inclusion criteria mentioned in the Polish therapeutic program for treatment with abiraterone in patients with docetaxel-naïve, castration-resistant prostate cancer are more restrictive than seemed to be judged based on published data. The re-

Table 1. The inclusion/exclusion criteria of the NFZ abiraterone acetate therapeutic program in the first-line treatment of patients with prostate cancer (chemotherapy-naïve population) and tests required before and during the treatment

Inclusion criteria	Exclusion criteria	Withdrawal criteria for therapeutic program	Test results required at enrolment to therapeutic program	Treatment monitoring
1. Histologically confirmed adenocarcinoma of the prostate 2. Lack of clinical indications for chemotherapy 3. Castration-resistance status confirmed based on serum testosterone level of less than 50 ng/dl (1.7 nmol/l or less) in patients with disease progression according to criteria listed in section 4 of therapeutic programme) 4. Disease progression based on: — three consecutive rises of serum PSA level in tests performed at least 2 weeks apart with proved 2 rises by 50% from baseline value (nadir), with nominal value of PSA level > 2 ng/ml or — occurrence of radiographic disease progression (skeleton, visceral organs, soft tissue) 5. Gleason score < 8 based on tumor sample histology testing 6. No opioids use required to control the symptoms of prostate cancer (history of opioids use allowed) 7. Performance status 0 according to WHO classification 8. Age 18 years or older All inclusion criteria must be fulfilled	1. Hypersensitivity to active substance or any of excipient/vehicle substance 2. Mild or severe liver function disorders (class B or C according to Child-Pugh criteria) 3. Aminotransferases activity equal or higher than 2.5-fold upper of normal limit; potassium concentration below lower limit of normal range 4. History of ketoconazole use in treatment of prostate cancer for period of time longer than 7 days 5. Uncontrolled heart disease or circulatory system disease, uncontrolled hypertension 6. Diagnosis of small-cell prostate cancer	1. Appearance of hypersensitivity to abiraterone acetate or any of excipient/vehicle substance 2. Progressive disease during treatment with the drug defined according to criteria as follows: — appearance of at least two out of three of following types of progression: • clinical progression: — pain progression defined as need for *de novo* introduction of opioid for period of time longer than 2 weeks (except the situation when the intention for the introduction of opioid analgesics was the treatment of adverse event related to a drug used previously) or — presentation of skeletal related events (SRE) or — deterioration of patient's performance status (according to WHO classification) to at least score 2 lasting at least for 2 weeks • PSA progression defined as three consecutive rises of serum PSA level in tests performed at least 1 week interval with proved 2 rises by 50% from baseline value (nadir), with nominal value of PSA level > 2 ng/ml • radiographic progression defined as appearance of at least two new lesions confirmed in radiographic examination, or — progression according to RECIST criteria 3. Emergence of adverse events that preclude the possibility to continue the treatment according to characteristic of drug product 4. Consent withdrawal by the patient	1. Histologically confirmed adenocarcinoma of the prostate 2. Baseline assessment of serum aminotransferases activity and other tests required for liver functional assessment according to Child-Pugh criteria at baseline 3. Bone scan (if not performer previously) 4. Radiographic assessment (roentgenography or computer tomography or tomography of magnetic) according to clinical situation 5. PSA level and testosterone level testing	Every time if clinically indicated: 1. PSA level assessment every 3 months 2. Radiographic assessment depending on method of assessment used at 3. Assessment of aminotransferases activity every 2 weeks for the first 3 month of treatment and every 1 month thereafter 4. Other tests as clinically indicated 5. Bone scan after 6 months from beginning of the treatment or earlier if clinical progression present according to enclosed criteria of progression

striction of abiraterone acetate use only to patients with asymptomatic clinical course of the disease (ECOG 0) — including men without pain related to metastatic spread to skeleton — is based on sub-group analysis of the COU-AA-302 study only. It seems to be contradictory to rules of interpreting scientific data. What is even more important — it does not reflect the veritable clinical practice. Similarly, restrictions regarding abiraterone use to patients with Gleason < 8 prostate cancer have no strong scientific rationale. These are contrary to post-hoc analysis data [13] and reflect the lack of payor consistence during the creation of the therapeutic program procedure.

Despite convincing data from a prospective, randomised, multicentre, phase III clinical trial (PREVAIL) [14], enzalutamide is still excluded from the therapeutic program in chemo-naïve patients. The drug is a novel antiandrogen with higher affinity to androgen receptor when compared to flutamide or bicalutamide, and it is lacking in agonistic activity, while characterised by more complex molecular mechanism of action. In the population of mildly-symptomatic, chemotherapy-naive patients with castration-resistant prostate cancer the drug, in a statistically and clinically significant manner, improves median time to progression or death, time to chemotherapy, time to deterioration of quality of life, and overall survival.

Radium dichloride Ra-223 is a therapeutic option mentioned in the program "The treatment of castration-resistant prostate cancer". In the prospective, randomised, multicentre, phase III clinical trial ALSYMPCA [15] the drug, compared to placebo, statistically improved overall survival (the median OS 14.9 months *vs.* 11.3 months; HR: 0.70; 95% CI: 0.58–0.83; $p < 0.001$) and proved its advantage in terms of all protocol secondary end-points predefined by the study [statistically significant prolongation of time to the first skeletal-related event (SRE), time to increase of PSA] in the population of patients with metastatic involvement restricted to the skeleton. The therapeutic program allows the use of Ra-223 in the first-line treatment of castration-resistant prostate cancer if there is a documented contraindication for docetaxel use.

You can learn more about formal, logistic, and financial restrictions of treatment with alpharadin in the chapter dedicated to part of the therapeutic program, describing the second-line systemic treatment of CRPC („Oncology in Clinical Practice" No. 3).

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