Review article

The role of enzalutamide in the treatment of prostate cancer from the perspective of Polish oncologists

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ABSTRACT

For several years, prostate cancer has remained the most common malignancy in male patients in Poland. A large number of patients combined with rising costs of therapy translate into a significant socio-economic burden. In a clinical oncologist's practice, we usually deal with patients with advanced prostate cancer. Taking into account the poorer prognosis in advanced disease, development of new therapeutic options as well we their adequate selection is of paramount importance. Enzalutamide is one of the second-generation androgen axis inhibitors, which has the ability to overcome resistance to androgen deprivation therapy by inhibiting the androgen-DNA signalling on several levels. Its efficacy and safety had been proven in numerous phase II and phase III clinical studies and it has been registered by regulatory authorities in the United States and European Union in the treatment of mCRPC, mCSPC and nmCRPC. In this article selected issues related to the treatment of prostate cancer are discussed, with particular emphasis on the role of enzalutamide (including its mechanism of action, indications, efficacy and safety).

Key words: enzalutamide, prostate cancer, hormonotherapy, anti-androgen, second-generation androgen axis inhibitor, therapy, castration resistance, metastatic, non-metastatic, Polish perspective

IS PROSTATE CANCER A SIGNIFICANT MEDICAL PROBLEM?

In order to gain a better insight into the problem, it is worth observing that in 2020 over 19 million patients were diagnosed with malignant tumours across the world. Male patients constituted more than a half of them (10 million), with prostate cancer as the second most common malignancy at the time (1.4 million patients). The highest incidence was reported in countries with very high human development index [1]. It is estimated that by 2040 the incidence will have risen by ca. 1 mln/year, with almost double the mortality (from ca. 375 000 to ca. 740 000/year). The higher frequency of PSA (prostate specific antigen) tests, and (indirectly) the higher number of biopsies are amongst the factors which have contributed to an increase in the detection of the disease. Experts also point out that overdiagnosis may also be a problem, and that there are important psychosocial aspects related to the condition [2, 3]. For several years, prostate cancer has remained the most common malignancy in male patients in Poland (over 17 000 newly diagnosed patients in 2019) [4]. Early diagnosis is still of fundamental prognostic significance, enabling the implementation of efficacious local radical treatment. At the same time, the role of active surveillance in selected patient groups is emphasised. Disease recurrence, and in particular detection of metastatic disease is associated with poorer prognosis. A large number of patients combined with rising costs of therapy translate into a significant socio-economic burden [5].

WHAT ARE THE BASIC MECHANISMS ASSOCIATED WITH THE DEVELOPMENT OF PROSTATE CANCER?

Before we look into the mechanisms behind the development of the tumour, it is worth listing the risk factors of prostate cancer, as some of them explain the pathways of prostate cancer evolution to some extent.

The primary risk factors include patient age and race (Afro-American). Apart from those, there are several less frequent and less evident factors which may be conducive to prostate cancer, including, inter alia, some genetic disorders, a family history of prostate cancer, and eating habits that lead to obesity. Even though the well-known mutations responsible for the development of different cancers (e.g. *BRCA* gene mutations) spark great emotion, one should remember that they only account for a small percentage of cases (ca. 10%).

What are the specific mechanisms behind the development of prostate cancer? Why do patients develop prostate cancer? Response to those questions (if ever offered) will certainly be worth the Nobel Prize.

We can (so far only passively) observe that in nearly all males, the microscopic image of the prostate gland changes with age; from small changes to the gland structure, referred to as PIN (prostatic intraepithelial neoplasia), all the way to prostate cancer, whose biological aggressiveness is measure with the help of the Gleason score, i.e. the visual difference between the tumour tissue pattern and a normal image of the prostate gland. The evolution is accompanied by numerous mutations, including the *PTEN* and *TP53* gene mutations [6].

Androgens, inflammatory and genetic factors, and likely many other factors are involved in the development of prostate cancer. Taking into consideration how common it is that prostate cancer is detected in postmortem specimens (performed for any reason), the question asked should not be "if" a male patient is likely to develop prostate cancer, but "when" it happens.

WHAT IS CASTRATION RESISTANCE AND HOW IMPORTANT IS IT?

Castration resistance is defined as the situation, in which prostate cancer advances despite the maintenance of castrate testosterone levels, achieved with pharmacological methods (ADT, androgen deprivation therapy) or surgery (orchidectomy). Prostate cancer progression is defined as increased PSA levels and/or the occurrence of new metastases. Castration resistance mechanisms of prostate cancer are not fully known, but the most significant involve changes in the structure and function of the androgen receptor in cancer cells, and emergence of cells within the tumour, whose growth and proliferation is completely independent of androgens, e.g. neuroendocrine differentiation cells.

From a clinical perspective, castrate resistant disease affects both patients with relatively good prognosis, i.e. patients with no metastatic lesions and slow PSA increase, or PSA doubling time (PSA-DT) of more than 10 months, as well as those patients whose survival does not exceed several months (patients with distant metastases, following several lines of treatment).

Treating castration resistant prostate cancer is a considerable challenge for the physicians and the patients alike, particularly in light of the specific features of the population, including older age, cardiovascular diseases, and concomitant medications. Presently, two therapeutic methods play important roles in the treatment of patients with metastatic castrate-resistant prostate cancer

(mCRPC): chemotherapy and second-generation antiandrogens. Docetaxel was the first drug to prolong the life of patients with mCRPC. Cabazitaxel, which is currently not reimbursed in Poland, turned out to be efficacious in patients who had progressed on second-generation antiandrogens or abiraterone acetate. The advantage of chemotherapy stems from its mechanism of action, which is not associated with androgen receptors, whereas its disadvantage is the significantly higher toxicity of therapy. Hence, the addition of other less toxic therapies to clinical practice, including enzalutamide and other second-generation antiandrogens, is so important.

WHAT IS THE PLACE OF ENZALUTAMIDE IN THE THERAPY OF PROSTATE CANCER IN CONTEMPORARY CLINICAL PRACTICE?

In a clinical oncologist's practice, we usually deal with patients with advanced prostate cancer, and in particular with the metastatic castrate-sensitive prostate cancer (mCSPC, also referred as the metastatic hormone-sensitive prostate cancer, mHSPC), with non-metastatic castrate-resistant prostate-cancer (nmCRPC/M0 CRPC), and especially with the metastatic castrate-resistant prostate cancer (mCRPC). Taking into account the poorer prognosis in advanced disease, development of new therapeutic options as well we their adequate selection is of paramount importance. Amongst the therapeutic options recently introduced in Poland, second-generation androgen axis inhibitors (NHT, novel hormonal therapies), and radium-223 dichloride, a radiopharmaceutical with calcimimetic properties, deserve special attention. Unfortunately, there is no universal access to cabazitaxel or PARP inhibitors [7]. Enzalutamide, one of NHTs, has been investigated as part of many phase III clinical trials, and it has been registered by regulatory authorities in the United States and European Union in the treatment of mCRPC, mCSPC and nmCRPC. In Poland, NHT therapy is not presently reimbursed for the treatment of mCSPC.

EVIDENCE FOR THE EFFICACY OF ENZALUTAMIDE THERAPY

Efficacy and safety of enzalutamide, which was developed in 2009, have been proven in numerous phase II and phase III randomized, blinded, placebo-controlled clinical studies, and active-comparator studies, involving patients suffering from mHSPC, nmCRPC and mCRPC. Results of the ARCHES phase III trial indicate that the use of enzalutamide combined with ADT prolongs radiographic progression-free survival (rPFS; primary endpoint) by an estimated time of 11 months in the mHSPC population. The use of the drug also contributes to a statistically significant reduction in the risk of mortality, by 34%, as compared to the use of ADT solely. Overall survival (OS) constituted a secondary endpoint in the study, and median OS has not yet been reached in either of the study arms [8]. In the PROSPER clinical trial, it was demonstrated that the use of enzalutamide in M0 CRPC patients led to a prolonged median metastasis-free survival (MFS) and OS, as compared to placebo (reduction in the risk of death by 27%) [9].

Benefits, in terms of OS, stemming from the use of enzalutamide in the mCRPC population have also been demonstrated, both at the stage before chemotherapy (median difference of 5 months after a 5-year follow-up period) [10] as well as at the stage of progression following chemotherapy (survival improved by 4.8 months as indicated in the AFFIRM trial) [11].

In the STRIVE phase II clinical study, superiority of enzalutamide was demonstrated over bicalutamide, a first-generation antiandrogen, expressed as a statistically significant extension of the progression-free survival (PFS) by 13.7 months (i.e. 19.4 vs. 5.7 months). In the population of patients with newly diagnosed CRPC (with and without metastases). Similar results were reported in the TERRAIN phase II clinical trial (PFS of 15.7 vs. 5.8 months, respectively), involving patients with mCRPC only [12, 13].

WHAT IS THE MECHANISM OF ACTION OF ENZALUTAMIDE?

As mentioned before, with time, resistance to ADT treatment develops as a result of changes in the structure and function of the androgen receptor (AR), among other reasons. Enzalutamide is a second-generation antiandrogen, and as such it has the ability to overcome resistance to ADT. Its mechanism of action consists in inhibiting the androgen-DNA signalling pathway that is responsible for androgen-dependent proliferation of cancer cells. It occurs on several levels. First, enzalutamide inhibits androgen binding to AR. Secondly, it blocks the nuclear translocation of the active androgen-receptor complex, and blocks the binding of the active androgen-receptor complex to DNA in the cell nucleus. All of that leads to inhibited proliferation of cancer cells [14].

HOW IS ENZALUTAMIDE ADMINISTERED, AND WHAT DO WE KNOW ABOUT ITS SAFETY?

General dosing principles

The dosing scheme of enzalutamide was determined in the course of clinical trials, and is described in detail in the Summary of Product Characteristics (SPC). The drug has been available in

Poland in the form of capsules, and recently also in the form of tablets (40 mg ones in both cases). It should be taken once daily, at a total dose of 160 mg, irrespectively of the meal [15].

What are the most common adverse reactions?

The most commonly reported adverse effects listed in the SPC include fatigue, hot flushes, arterial hypertension, fractures and falls. Cognitive function disturbances have also been observed, as have seizures, and the rare posterior reversible encephalopathy syndrome.

When should the dose be reduced?

In accordance with the SPC, in the case of adverse reactions that are difficult for the patient to tolerate, and grade 3 or higher symptoms of toxicity, the treatment should be discontinued for a week or until the symptoms resolve to a grade lower than 3. Treatment continuation is possible at the original dose or at the dose reduced to 120 mg or 80 mg. In our clinical practice, we rarely encounter situations, where enzalutamide dose modification is necessary. In line with the SPC, if strong CYP2C8 inhibitors need to be administered concurrently with enzalutamide, the drug should be dosed at 80 mg. It is not necessary to reduce the dose in elderly patients or in patients with severe kidney or liver dysfunction.

What do we know about the drug-to-drug interactions of enzalutamide?

Enzalutamide is shown in interact with numerous medications. Its impact on metabolism may persist for a month or longer after its discontinuation due to its long half-life (nearly 6 days). As a strong CYP3A4 inductor and moderate CYP2C9 and CYP2C19 inductor, it may reduce the efficacy of other medicinal products. In accordance with the SPC, enzalutamide should not be combined with antithrombotic medications metabolized by CYP2C9 (acenocoumarol, warfarin). If such therapy is necessary, the prothrombin time (INR) should additionally be monitored. As enzalutamide itself is metabolized by CYP2C8, its blood serum levels may be higher, when strong inhibitors of the cytochrome (e.g. pioglitazone) are administered at the same time, and lower, when the patient received one of CYP2C8 inductors. Some of the more common drug–drug interactions include those with, i.e. immunosuppressants (e.g. cyclosporine, tacrolimus), antivirals (e.g. atazanavir), antifungals (itraconazole), anticoagulants (e.g. rivaroxaban), antiplatelets (clopidogrel), and centrally acting medicines that are quite frequently taken by prostate cancer patients such as fentanyl or buprenorphine (metabolized with the involvement of CYP3A4). Hence, it is of utmost importance to review all the medications received by the patient, as recommended in the SPC. A detailed discussion of cardiovascular aspects goes beyond the scope of this paper, but it should be remembered that in some patient groups, data on the administration of enzalutamide are limited. Indeed, patients with severe cardiovascular conditions were not qualified for the phase III clinical trials, e.g. patients with NYHA > II heart failure (unless their left ventricular ejection fraction was at least 45%), patients with unstable angina, those with a history of myocardial infarction (up to 3 and 6 months before qualification, respectively) as well as patients with bradycardia, and untreated or treatment refractory arterial hypertension [15–17].

WHEN SHOULD A UROLOGIST AND RADIOTHERAPIST REFER A PATIENT TO A CLINICAL ONCOLOGIST?

The answer to the question is not obvious, as it is not the case that a clinical oncologist has something to offer to the patient at any stage of disease progression. Generally speaking, it is highly justified to refer the patient to a clinical oncologist, when the patient's PSA keeps rising and/or metastases to the bones or other organs have been detected. In our opinion, it is necessary to refer the patient to an oncologist in the following situations:

Patients suffering from castration-sensitive prostate cancer with distant metastases. Apart from ADT, other forms of pharmacotherapy should be considered in the patient, including chemotherapy or addition of second-generation antiandrogen or abiraterone acetate. Even though only chemotherapy is reimbursed in Poland at the moment, one can expect that other therapeutic options will be available soon (e.g. thanks to the reduced prices of generic drugs). Moreover, in patients with a low disease burden, prostate and lymph node radiotherapy is an option worth considering.

Patients suffering from castration-resistant prostate cancer. In such a situation, it is practically of no significance, whether distant metastases have developed or not in the patient. In that particular population of patients, one is obliged to consider other therapies beyond ADT, as castration-resistant prostate cancer is a much more dynamic disease that prostate cancer that is sensitive to androgen deprivation.

If, in the course of ADT (despite castrate levels of testosterone), PSA levels continue to rise, and there are no distant metastases detected (in CT and bone scintigraphy), the patient should be referred to an oncologist, as there are better therapeutic options out there than, e.g., bicalutamide. Patients who suffer from castration-resistant prostate cancer without metastases (so-called M0 patients) have recently been covered by a reimbursement scheme in Poland, involving the treatment based on second-generation

antiandrogens (enzalutamide, apalutamide, darolutamide). One should remember that not every patient from that group requires treatment; with the fundamental indication for treatment being the PSA-DT below 10 months.

Finally, the last group of patients who must be seen by a clinical oncologist are patients who suffer from mCRPC. If there are no contraindications for treatment, there are several forms of survival prolonging therapies. Most of them are available and reimbursed in Poland. What we have in mind here is not just novel hormonal therapy, but also chemotherapy, radiopharmaceuticals, and drugs which target bone metastases.

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