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REVIEW ARTICLE

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Evolution of prostate cancer therapy. Part 1

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ABSTRACT

Prostate cancer is the most common cancer in men. Strategies relying on androgen deprivation have long been utilized in it's treatment. However, the therapy of castration-resistant disease still remains challenging. Therapeu-tic options have rapidly evolved during the last decade. New molecules with unprecedented activity, provided significant survival benefit in advanced disease. This review presents the key aspects of prostate cancer systemic therapy evolution over the last decades. The first part focuses on therapies active in castration-resistant disease. Part two reviews data on earlier therapy lines and principles relevant to devising optimal treatment sequence.

Key words: prostate cancer, castration-resistant, mCRPC, abiraterone, apalutamide, enzalutamide

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Introduction

In 1853, British surgeon John Adams described in the *Lancet* a case of a cirrhotic prostate gland with associated pelvic and lumbar lymphadenopathy. This case report is cited as the first-ever prostate cancer description [1]. Although Adams believed that the described disease was very rare, nowadays prostate cancer is the most common malignant tumour among men. In 2018, overall 1.28 million new cases were reported, and 0.38 million men died from the disease [2].

The relation between castration and secondary sexual characteristics has been known since antiquity. The scientific description of the effect of castration on prostate volume in animals was first published by James William White in 1893 [3]. In 1935, at intervals of several months, three researchers: Ernst Laqueur, Adolf Butenandt and Lavoslav Ružička, independently described the chemical structure of testosterone, initiating work on its role in mammalian physiology. In 1939, Butenandt and Ružička were awarded the Nobel Prize for their discovery. In 1941, Charles Huggins and Clarence Hodges jointly described the beneficial effects of surgical castration and oestrogen therapy on the course of metastatic prostate cancer [4]. Huggins continued his research in this area over the years, paving the way to modern systemic therapy of this cancer, for which he was also awarded the Nobel Prize in 1966. In 1969, Mainwaring et al. [5] discovered the androgen receptor (AR), which soon led to the description of its first inhibitor — cyproterone. In 1971, Andrew Schally described the structure and function of the gonadotropin-releasing hormone (GnRH) and its importance for the regulation of sex hormones [6]. In 1973–1976, long-acting analogues of this hormone were discovered, which were already registered as medicinal products in 1984–1987. During the next decade, further AR antagonists emerged with a more favourable therapeutic index.

The pathogenesis of prostate cancer is inextricably linked with AR. The management of pathological hormonal stimulation, as well as the mechanisms of cancer cell resistance to ADT, is the key to effective cancer therapy. Therapeutic options have therefore evolved from surgical through pharmacological castration to pharmaceuticals designed to counteract the molecular mechanisms that determine the development of castration resistance.

In this two-part review, the authors summarize the course of this evolution. They present the results of

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ground-breaking research and indicate the most important, in the authors' opinion, directions for the further development of systemic treatment of patients with prostate cancer. The first part discusses the mechanisms of action of key drug classes and the data on their efficacy in metastatic, castration-resistant prostate cancer. Systemic treatment options in patients with castration-sensitive metastatic prostate cancer and patients with non-metastatic, castration-resistant cancer are presented in the second part, while discussing methods of optimizing sequential pharmacotherapy. It is in hope that it will allow the reader to better understand the landscape of available therapeutic options and the direction in which it is evolving, as well as facilitate decision-making in clinical practice.

Androgens and prostate cancer

Similarly to healthy prostate acinar and ductal cells, prostate cancer cells in untreated patients almost always express AR. It is a cytoplasmic protein, coded on the X chromosome and composed of several domains, including ligand-binding domain (LBD) and DNA binding domain (DBD). The inactive AR forms a complex with heat shock proteins (HSPs) 40, 70 and 90, which stabilize the receptor and prevent its proteolysis. Lipophilic androgens diffuse relatively easily across the cell membrane where they bind to the AR. This results in a two-time change in the receptor conformation and unbinding of HSP. This is followed by AR nuclear translocation mediated by the microtubular cytoskeleton. The AR displaced into the nucleus undergo homodimerization catalysed by nuclear coactivators, which leads to obtaining transcriptional activity by such a dimer, which in turn stimulates numerous genes promoters. AR activity determines the activation of several key mechanisms contributing to the carcinogenesis of prostate cancer and some other malignancies. This increases the proliferative drive, stimulates the secretory function, and neoangiogenesis (Fig. 1).

The androgens production in the male body is regulated by the activity of the hypothalamic-pituitary-gonadal (HPG) axis. Pulsatile changes of GnRH level in the hypothalamic-pituitary circulation cause the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). LH stimulates testosterone production by the Leydig cells of the testes, and FSH increases the production of plasma androgen binding protein (ABP). Androstenedione and dehydroepiandrosterone (DHEA) produced in adrenal glands, accounting for 10% of circulating androgens indicate a lower binding affinity for AR than testosterone. Their production, however, does not depend on the hormonal activity of the gonadal stimulating axis, but takes place constitutively, as it were, together with glucocorticosteroids synthesis. The androgen with the strongest affinity for AR is dihydrotestosterone (DHT), which is formed in the tissues: either from testosterone by the action of 5α-reductase (5AR) or from DHEA by the action of 17-hydroxylase/17.20-lyase (CYP17A1). There are two subtypes of the 5AR: the first is less active but is commonly present in various androgen-sensitive tissues, the second is more active, almost exclusively present in the prostate, making this organ extremely sensitive to androgen activity [7, 8].

The primary therapeutic approach in prostate cancer is androgen deprivation, which can be achieved in several ways. Bilateral orchiectomy or suppression of LH production by the pituitary gland can shut down testicular hormone production. Long-acting GnRH analogs (leuprorelin, goserelin, triptorelin) disrupt the natural rhythmic pattern of pulsatile GnRH secretion. In the initial phase, they cause the release of FSH and LH from the pituitary gland, which in turn causes an increase in testosterone concentration (the so-called flare-up phenomenon), but the final outcome is a durable HPG axis blockade. In turn, GnRH antagonists (abarelix, degarelix and oral relugolix) immediately inhibit the secretion of gonadotropic hormones, which prevents the flare-up effect. Other strategies of hormone therapy include substances that competitively block AR (bicalutamide, flutamide, nilutamide), antagonize its activity (oestrogens), and inhibit the conversion of androgens to DHT (finasteride, dutasteride, epristeride) (Tab. 1).

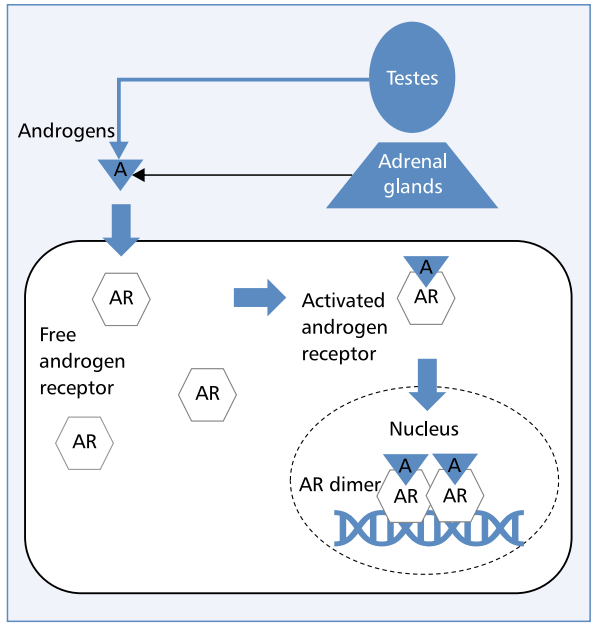

Figure 1. Androgen receptor-dependent signalling in a castration-sensitive prostate cancer cell; A — androgens; AR — androgen receptor

Table 1. Strategies affecting AR-dependent signalling pathways

Blocking androgen synthesis in the testes	Leuprorelin Goserelin Triptorelin Abarelix Degarelix Relugolix
Blocking androgens production in the adrenal glands	Glucocorticosteroids Adrenalectomy
Blocking enzymes responsible for androgen synthesis (adrenal, paracrine, autocrine)	Abiraterone Acetate Ketoconazole Aminoglutethimide
Blocking androgen conversion	Finasteride Dutasteride Epristeride
Reversing the androgen effect	Oestrogens
Inhibiting the binding of androgens to the receptor	Bicalutamide Flutamide Nilutamide Cyproterone Acetate Spironolactone
Multi-point blocking of androgen receptor activity	Enzalutamide Darolutamide Apalutamide
Blocking AR translocation	Docetaxel Cabazitaxel

Castration-resistant prostate cancer

The classic anti-androgen therapies described above have been and are successfully used in the treatment of patients with advanced prostate cancer. However, it should be remembered that in the case of prostate cancer, as with any other advanced neoplasms exposed to the long-term hormone therapy, there is always a loss of sensitivity to previously active hormone therapy. Historically, this condition was called hormone resistance, but today it is already known that at this stage of the disease, AR is still active and strongly promotes the progression of the neoplastic process. Thus, a more precise term has become widespread: castration-resistant prostate cancer (CRPC). The definition of castration resistance includes the occurrence of PSA increase and/or imaging progression during the effective castration confirmed by the testosterone level < 50 ng/dL (1.7 nmol/L). Most patients suffer from metastatic cancer at the time of resistance occurrence, but castration resistance can also be determined based on an increased PSA level alone without evidence of image progression. To meet the non-metastatic CRPC definition adopted by most societies, PSA increase must meet 3 conditions simultaneously: 1. three consecutive PSA increases separated by at least one week; 2. two increased values must be at least 50% higher than the nadir; 3. nominal PSA value must be > 2 ng/mL.

Knowing the molecular phenomena that determine castration resistance it is necessary to understand the mechanisms of action of drugs active for CRPC. First, as previously mentioned, the adrenal glands consistently produce small amounts of androgens in castrated patients. Additionally, in cancer cells or the tumour microenvironment, ectopic androgen production may occur. Moreover, the AR itself may be amplified, overexpressed, or activated by first-generation anti-androgen drugs. There may also be AR variants with increased affinity for the ligand or with constitutive, ligand-independent activity at all, arising from mutation or alternative AR DNA splicing. AR activity may also increase as a result of receptor phosphorylation by kinases associated with AR-independent signal transduction pathways from membrane receptors or as a result of increased expression of nuclear coactivators [9] (Fig. 2).

Therapies effective in overcoming castration resistance include cytotoxic drugs from the taxoid group; new generation anti-androgens that prevent the functioning of typical resistance mechanisms (apalutamide, darolutamide, enzalutamide, abiraterone acetate); radiopharmaceutical — radium-223; more recently PARP inhibitors (PARPi); and finally immunotherapeutics, of which, so far, only specific, active immunotherapy based on dendritic cells has proven effectiveness.

Chemotherapy

Until the end of the 20th century, no drugs were available to improve the prognosis of patients with CRPC. In the 1990s, strategies for prolonging progression-free survival emerged — those were estramustine, mitoxantrone or inhibition of adrenal androgen production with glucocorticosteroids.

The first drug that significantly improved the prognosis of patients with metastatic CRPC (mCRPC) was docetaxel — a synthetic derivative of paclitaxel, obtained from the tissues of European yew. Docetaxel was first described in the 1980s. Its mechanism of action, as in the case of other taxoids, is to stabilize microtubules by binding to β-subunit of tubulin [10]. The resulting dysfunction of the karyokinetic spindle is considered to be the main mechanism of action of taxoids. There are also data indicating additional mechanisms: inhibition of oncogenic kinases from the *BCL* family and disruption of activated AR nuclear translocation mediated by the microtubular cytoskeleton [11]. In 2000–2002, overall 1,006 men with mCRPC were enrolled in TAX-327 study [12, 13]. Patients were randomized in a 1:1:1 ratio to the group receiving: mitoxantrone (12 mg/m^2 q3w), docetaxel

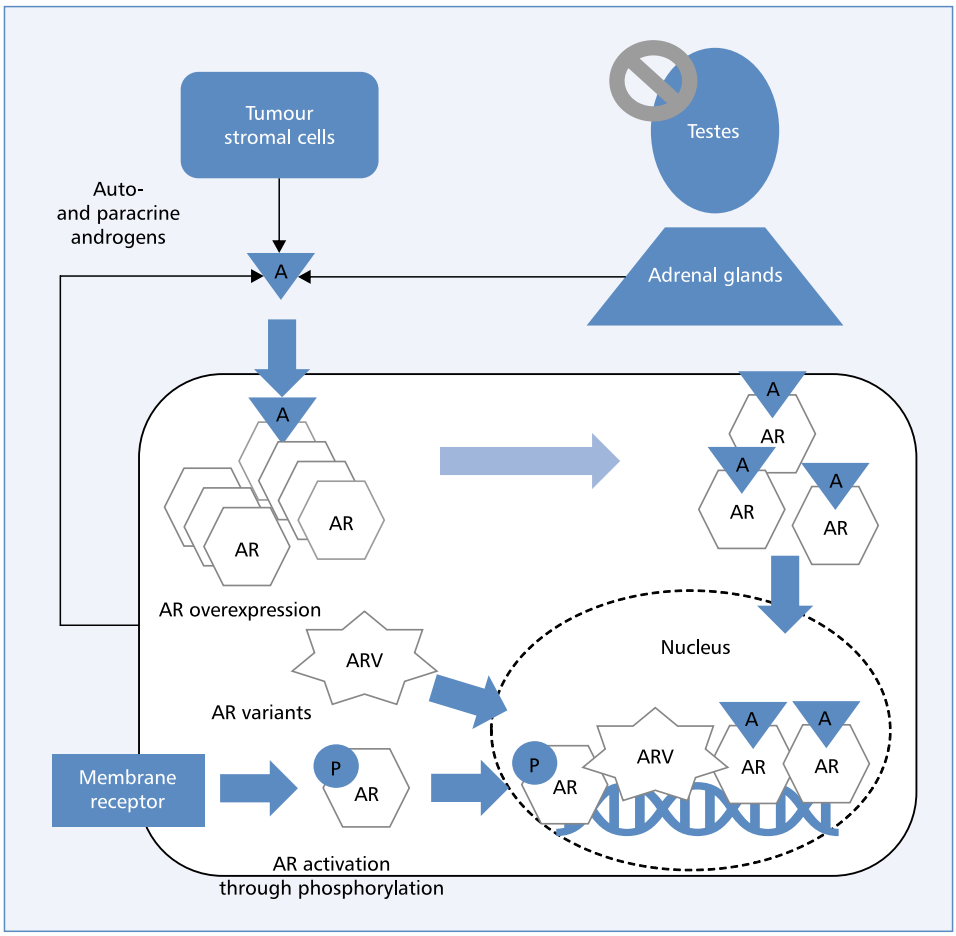

Figure 2. Mechanisms of castration resistance in the prostate cancer cell; A — androgens; AR — androgen receptor; ARV — AR variants

(75 mg/m^2 q3w) or docetaxel (30 mg/m^2 q1w). All patients also received a suppressive dose of prednisone (5 mg bid). The high dose docetaxel arm compared with the control arm showed a significant reduction in the relative risk of death by 21% [hazard ratio (HR) 0.79; 95% confidence interval (CI): 0.67–0.93; p = 0.004] with median overall survival (OS) of 19.2 months and 16.3 months, respectively. A low dose of weekly docetaxel was not associated with a significant prognosis improvement (median OS 17.8 months). Both PFS, objective response rate (ORR) and quality of life parameters were more favourable in patients receiving high dose docetaxel. Docetaxel was associated with a higher risk of neutropenia (32% *vs.* 22%), but not with febrile neutropenia or other cytopenias. Docetaxel also caused more gastrointestinal symptoms as well as neurotoxicity and skin toxicity, with a lower risk of hepatotoxicity than mitoxantrone. Subgroup analyses showed that patients who benefited most from the therapy were asymptomatic or with low symptoms intensity [The Functional Assessment of Cancer Therapy-Prostate (FACT-P) < 109], with no pain, in good performance status (PS) (KPS ≥ 90%), with no visceral metastases and high PSA levels (≥ 115 ng/mL). It can therefore be concluded that docetaxel-based therapy is best initiated in the early stages of mCRPC.

Cabazitaxel, first described in 1999, is a taxoid with a chemical structure and mechanism of action analogous to docetaxel. It has been designed to bypass the typical resistance mechanisms to classic taxanes that appear in cancer cells exposed to paclitaxel or docetaxel. In particular, cabazitaxel has no affinity for P-glycoprotein — a protein with transmembrane transporter activity — that actively removes xenobiotics (including docetaxel) from inside the tumour cell [14]. In 2010, the results of a phase III TROPIC study [15] were published, which assessed the effectiveness of cabazitaxel in mCRPC patients after failure of docetaxel treatment. In this study, 755 patients were randomized in a 1:1 ratio to either 25 mg/m^2 cabazitaxel or 12 mg/m^2 mitoxantrone, with both arms receiving a suppressive dose of prednisone. The study met its primary endpoint: it showed a significant reduction in the relative risk of death by 30% (HR = 0.70 95% CI: 0.59–0.83; p = 0.0001) with a median OS of 15.1 months (cabazitaxel) *vs.* 12.7 months

(mitoxantrone). Treatment in the experimental arm was clearly more toxic compared to the control arm. Adverse reactions were reported in 94% and 88% of patients, respectively, and CTCAE Grade ≥ 3 adverse events (AEs) in 82% and 58% patients in cabazitaxel and mitoxantrone arm, respectively.

It was widely believed that the development of new antiandrogens (discussed later) would diminish the position of cabazitaxel in a multi-step treatment strategy in mCRPC patients. It turns out, however, that this drug remains effective in subsequent lines of treatment. In September 2019, Ronald de Wit et al. [16] published in the NEJM the results of a phase IV CARD study [17], including 255 mCRPC patients who failed treatment with docetaxel and one of the new antiandrogens (abiraterone acetate or enzalutamide) used in any sequence. Patients were randomized in a 1:1 ratio to the cabazitaxel arm (25 mg/m^2 q3w) in combination with prednisone or the arm with a new generation of a previously unused hormonal drug (enzalutamide 160 mg/day or abiraterone acetate 1000 mg/day). The primary endpoint was radiological progression-free survival (rPFS). The secondary endpoints included, among others: OS, time to occurrence of skeletal events, and quality of life parameters.

The study met its primary endpoint. The median rPFS was 8.0 months for cabazitaxel and 3.7 months for the next-generation hormonal drug (HR = 0.54; 95% CI: 0.40–0.73; p < 0.001). The benefit of cabazitaxel was observed in all subgroups defined in the study, and in particular, no dependence of the activity of this drug on the previously used hormonal drug (enzalutamide *vs.* abiraterone) was demonstrated. The median OS was 13.6 months in the cabazitaxel arm and 11.0 months in the control arm, which translated into a significant reduction in the relative risk of death by 36% (HR = 0.64; 95% CI, 0.46–0.89; p < 0.008). After progression, 23.3% of patients in the active arm received a previously unused new anti-androgen in the subsequent treatment line. Cabazitaxel in the subsequent line was received by 33.3% of patients from the control arm. Of the patients with measurable lesions at randomization, an objective response was achieved by 37% of patients in the cabazitaxel arm and 12% patients in the hormone therapy arm (p = 0.004). The toxicity profile was consistent with data from previous studies.

Androgen synthesis inhibitors

Research on the pharmacological suppression of adrenal androgen production has been continued since at least the 1960s when aminoglutethimide was discovered — a pleiotropic drug, blocking, inter alia, CYP11A1 — the key enzyme for the conversion of cholesterol into steroid hormones precursors (Fig. 3). Aminoglutethimide effectively blocks the production of all steroid hormones, including glucocorticoid and mineralocorticoids, which in combination with its activity in other metabolic pathways, is responsible for its relatively high toxicity. In 2003–2007, ketoconazole (an antifungal imidazole derivative) activity was demonstrated in CRPC. This drug inhibits CYP11A1 and CYP17A — enzymes that block the conversion of gestagens to androgens. Suboptimal hormonal activity and the unfavourable safety profile of ketoconazole prevented the widespread use of this drug in clinical practice.

A milestone in the field of androgen synthesis inhibition was the introduction of second-generation anti-androgens, the first of which is abiraterone acetate, first described in 1995. While still not fully selective, by acting mainly by inhibiting CYP17A, it blocks the production of androgen precursors with a secondary induction of mineralocorticoids overproduction. Abiraterone is also a 5AR inhibitor, with glucocorticoid synthesis blocking effect, most likely dependent on CYP11B inhibition. Thus, during the use of abiraterone, glucocorticosteroids supplementation is necessary to prevent acute adrenal insufficiency (Fig. 3).

In the COU-AA-301 study, recruiting in 2008–2009, overall 1,195 mCRPC patients after treatment failure on docetaxel were randomized in a 2:1 ratio to prednisone treatment (5 mg bid) in combination with abiraterone acetate (1000 mg qd) or placebo. In August 2012, in "The Lancet" journal, Karim Fizazi et al. [18] published the final results of the COU-AA-301 study, showing a significant improvement in the prognosis of patients receiving abiraterone. The use of abiraterone reduced the relative risk of death compared to placebo by 26% (HR 0.74; 95% CI: 0.64–0.86; p = 0.0001) with a median OS of 15.8 *vs.* 11.2 months, respectively. Abiraterone benefits were also observed for other endpoints. The toxicity profile was favourable, and most adverse reactions, including those leading to treatment modification or discontinuation, occurred at similar rates in both arms. Adverse events more commonly observed in the active arm included fluid retention, oedema, hypokalaemia and urinary tract infections. The risk of hepatotoxicity did not differ significantly between the arms.

In 2013, Charles Ryan et al. [19, 20] published in the "NEJM" the results of the COU-AA-302 study, which investigated the efficacy of abiraterone in a population of asymptomatic or oligosymptomatic mCRPC patients without prior docetaxel treatment. Between 2009 and 2010, overall 1,088 patients were randomized to the abiraterone plus prednisone arm or the prednisone plus placebo arm. The co-primary endpoints were PFS and OS. Median OS differed significantly in favour of abiraterone: 34.7 months *vs.* 30.7 months, which translated into a 19% reduction in the relative risk of death

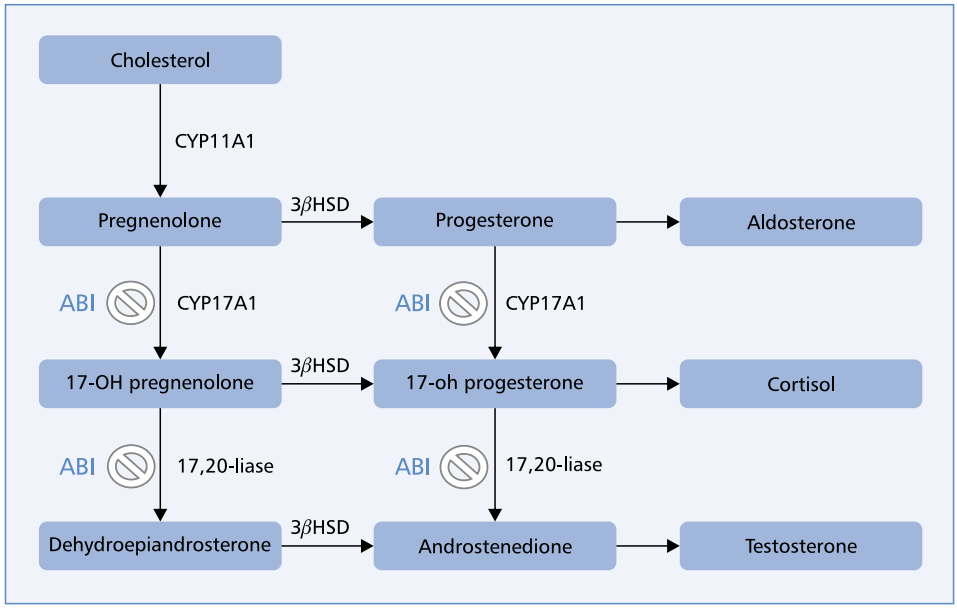

Figure 3. A simplified diagram of steroid hormone synthesis. Abiraterone mechanism of action

(HR = 0.81; 95% CI: 0.70–0.93; p = 0.0033). In the case of PFS [21], there was also a significantly higher median in the abiraterone arm — 16.5 months *vs.* 8.2 months (HR = 0.53; 95% CI: 0.45–0.61; p = 0.0001). More cardiovascular events, hepatotoxicity and hypertension were observed in the active arm.

Since 2012, enzalutamide (described in the next chapter) has been introduced in the indications analogous to those for abiraterone acetate. Although there is some competition between both medications, some researchers saw the potential in their combined use, due to the different mechanism of action.

At the American Society of Clinical Oncology (ASCO) 2018 Annual Meeting, Gerhardt Attard et al. [22] presented the results of the PLATO study, assessing the effectiveness of abiraterone in overcoming resistance to enzalutamide in a population of mCRPC patients who had not previously received chemotherapy with docetaxel. In the first step of the study, all patients received enzalutamide. Patients with primary resistance to this drug, as manifested by increased PSA level before the 21st week of therapy, were excluded from the study. The remaining patients at the time of PSA progression passed to stage II and were randomized in a 1:1 ratio to abiraterone in combination with enzalutamide or placebo. Therapy was continued until radiological progression or unacceptable toxicity. The primary endpoint was PFS. Of the 509 enrolled patients, 251 passed to the second stage (the reminded patients experienced no progression or did not meet the inclusion criteria). Median PFS did not differ significantly between the arms and was 5.7 months for the combination *vs.* 5.6 months for abiraterone monotherapy. There were no significant differences between other endpoints (including ORR). Combination therapy was associated with a higher risk of side effects (especially hypertension and hepatotoxicity).

At the ASCO 2019 Annual Meeting, Michael J. Morris et al. [23] presented the results of the phase III Alliance A031201 study, assessing the value of the combination of abiraterone and enzalutamide in the first-line mCRPC treatment. Prior treatment at the stage of castration sensitivity was allowed, including the early use of docetaxel. Patients included in the study were randomized in a 1:1 ratio to the combination of enzalutamide and abiraterone (+ prednisone) or enzalutamide monotherapy. Androgen deprivation was maintained in both groups. The primary endpoint was OS and the secondary endpoint was rPFS and biochemical response. From January 2014 to August 2016, overall 1,311 men were included in the study. There were no significant differences in OS: the median OS for the active and control arm was 32.7 months and 33.6 months, respectively, with combination therapy being more toxic.

New generation androgen receptor inhibitors

Enzalutamide, discovered in 2009, does not show partial agonist activity and binds the receptor more tightly than 1st generation AR inhibitors, reducing receptor affinity not only for its ligands. It also inhibits receptor nuclear translocation and the binding of AR to dimerization cofactors and DNA. The disadvantage of enzalutamide is the ability to penetrate the central nervous system and antagonize the receptors for

γ-aminobutyric acid (GABA) there, which can lead to neurological symptoms, in particular seizures.

In 2012, Howard Scher et al. [24] published in the "NEJM" the results of the phase III AFFIRM study, which assessed the effectiveness of enzalutamide in the treatment of mCRPC patients with imaging and/or biochemical progression after docetaxel therapy. In 2009–2010, overall 1,199 patients were randomized in a 2:1 ratio to treatment with enzalutamide at 160 mg/day or placebo. The study was terminated prematurely due to meeting its primary (OS) and secondary endpoints in the interim analysis. The median OS was 18.4 months (enzalutamide) and 13.6 months (placebo), respectively, which translated into a 37% reduction in the relative risk of death (HR = 0.63; 95% CI: 0.53–0.75; p = 0.001). The median rPFS was 8.3 months *vs.* 2.9 months in the experimental and control arm, respectively (HR = 0.25; p < 0.001); and radiological objective response rate was 29% *vs.* 4%, respectively. The overall incidence of adverse events did not differ significantly between the arms, and grade 3–4 toxicities were more frequent in the comparator arm. Seizures were observed only in the active arm, but only in 5 patients (0.6%).

In 2014, Tomasz Beer et al. [25] published in the "NEJM" the results of phase III PREVAIL study, assessing the effectiveness of enzalutamide in the treatment of mCRPC patients who had not been previously treated with docetaxel. In 2010–2012, overall 1,717 patients were randomized to enzalutamide 160 mg/day or placebo arm. The co-primary endpoints were PFS and OS. The study was terminated prematurely due to the proof of the test hypothesis in a stepwise analysis which showed an 81% reduction in the risk of disease progression or death and a 29% reduction in the risk of death in the enzalutamide arm. In the updated analysis presented in 2017 [26], the median PFS in the enzalutamide or placebo arms was 20.0 months and 5.4 months, respectively (HR = 0.32; 95% CI: 0.28–0.36; p < 0.0001), and median OS — 35.3 months and 31.3 months (HR = 0.77 95% CI: 0.67–0.88; p = 0.0002). In terms of the remaining endpoints, the superiority of the intervention was also demonstrated. The toxicity profile was comparable to the AFFIRM study, and enzalutamide was more commonly associated with fatigue, bone pain and diarrhoea, andropause symptoms, hypertension, and falls. Seizures were seen in one patient in each arm.

The advantage of enzalutamide over 1st generation antiandrogens was demonstrated in a randomized phase II STRIVE study, published in 2016. In this study, 396 patients with newly diagnosed CRPC (including 35% of patients without metastases) were randomized to the experimental arm with enzalutamide 160 mg/d or control arm with bicalutamide. For the primary endpoint (PFS — biochemical or radiological), a significant 76% reduction in relative risk was demonstrated, with a median PFS of 19.4 months (enzalutamide) *vs.* 5.7 months (bicalutamide) (HR = 0.24, 95% CI: 0.18–0.32; p = 0.001). For rPFS, a significant reduction in the risk of progression or death was also demonstrated with HR = 0.32 (95% CI: 0.21–0.50; p = 0.001), and a median of 5.7 months (bicalutamide) and not achieved in the enzalutamide arm.

Discovered in 2012, apalutamide is another next-generation anti-androgen with chemical and pharmacological properties similar to enzalutamide. This drug is characterized by a longer half-life, higher affinity for AR and lower permeability to CNS. The safety and activity of apalutamide were assessed in a phase I/II study (ARN-509-001) recruiting patients with mCRPC regardless of the number of prior systemic treatment lines. The results published in 2016 [27] indicated a comparable activity of apalutamide to enzalutamide.

Darolutamide is the newest, registered, second-generation anti-androgen with mechanisms of action analogous to those of apalutamide and enzalutamide. In contrast, however, darolutamide has antagonistic activity against some AR variants generated by mutations in the *AR* gene, making resistance development more difficult. Moreover, darolutamide is characterized by the strongest affinity for AR and the lowest CNS penetration compared to apalutamide and enzalutamide. The safety and activity of darolutamide were assessed in a phase I/II study (ARADES) including mCRPC patients in all treatment lines. The results of the study published in 2017 [28] confirmed that the activity of this drug is comparable to that of enzalutamide and apalutamide.

No further studies have been conducted with apalutamide and darolutamide in the treatment of mCRPC. Studies assessing the effectiveness of these drugs in the earlier stage of the disease will be presented in the second part of this review.

Radiopharmaceuticals

In the 1980s, systemic radiopharmaceuticals expanded the treatment armamentarium. Strontium-89, samarium-153, rhenium-186 and rhenium-188 emit mainly β-radiation with a tissue beam range of about 3 mm. The last three isotopes are also the source of gamma quanta, with an energy order of magnitude smaller, but with many times greater beam range. All of them have been shown to be effective in the treatment of bone metastases in the course of various cancers, but the benefit of their use is limited to symptoms alleviation (mainly pain intensity), without affecting the prognosis. The dose-limiting toxicity of all the above-mentioned radiopharmaceuticals is myelosuppression.

The desired characteristics of the isotope, which is to deliver a therapeutic dose of radiation in the area

of tumour bone remodelling, were defined relatively quickly. The uptake by the skeleton should be selective to avoid systemic toxicity and should have an optimal half-life: long enough to ensure a practical shelf life for the isotope, yet short enough to minimize dose retention and radiation safety related problems. Additionally, radioactive decay of the optimal radioisotope should be associated with emission of mainly α and β radiation, the low range of which in the tissues allows limiting myelotoxicity. Minimizing the emission of γ radiation significantly reduces the risk of systemic toxicity and eliminates problems related to radiological protection of people from the patient's surroundings. α radiation, due to the ease of energy transfer to molecules in tissues and causing mainly DNA double-stranded breaks (DSBs, is also much more effective in inducing cell death. It is estimated that already 1–4 "hits" on cellular DNA by the α particle are lethal for the cell, while in the case of β radiation nearly 1000 "hits" is needed [29].

Radium-223 was discovered in 1905 by Tadeusz Godlewski [30], a chemist associated with the Jagiellonian University. However, the anticancer potential of this isotope was only noticed at the end of the 20th century. All radium isotopes are calcimimetics — their electron shell mimics that of the calcium atom. Thus, both elements are characterized by a similar distribution in the body's tissues. After intravenous administration, radium is deposited primarily in the skeleton, showing a particularly high affinity for areas with the intense remodelling of the mineral matrix. Radioactive decay of radium-223 is associated almost exclusively with the emission of α radiation, with a small participation of β-decay (Fig. 4). The mechanism of action of the drug is primarily based on damaging the cancer cells DNA, but there are also data showing that it also modulates bone turnover, through toxic effects on osteoblasts and osteoclasts [31].

In 2013, Christopher Parker et al. [32, 33] published in the "NEJM" the results of the phase III ALSYMPCA study, which evaluated the effectiveness of radium-223 in the treatment of mCRPC patients with at least two symptomatic skeletal metastases. Participants could not have visceral or nodal metastases greater than 3 cm. In the case of patients without contraindications to the use of docetaxel, prior therapy with this drug was necessary. In 2008–2011, the study included 921 patients who were randomized in a 2:1 ratio to 6 doses of radium-223 (50 kBq/kg q4w) or placebo. After disease progression, patients in the placebo arm could receive radioisotope therapy. The primary endpoint of the study was OS and the secondary endpoints were time to first symptomatic skeletal-related event (SRE), time to PSA progression, and time to alkaline phosphatase progression. Radium treatment was associated with a significant reduction in the relative risk of death by 30% compared with placebo, with a median OS of 14.9 months (Radium-223) and 11.3 months (placebo) — HR = 0.70 (95% CI: 0.58–0.83; p = 0.001). The median time to SRE onset was 15.6 months (Radium-223) and 9.8 months (placebo); HR = 0.66 (95% CI: 0.52–0.83; p = 0.001). Additionally, a significant benefit of the use of Radium-223 was demonstrated in relation to the risk of PSA progression (HR = 0.64 95% CI: 0.54–0.77; p = 0.001) and alkaline phosphatase (HR = 0.17; 95% CI: 0.13–0.22; p = 0.001). In a subgroup analysis, the number of metastases ≥ 6 and the baseline alkaline phosphatase ≥ 200 U/L appeared to identify the patients who benefited most from the use of radioisotope. The incidence of adverse events, including serious and fatal ones, was slightly lower in the experimental arm. The most common side effects were cytopenia, bone pain, fatigue, nausea, and diarrhoea. There were no significant differences in the incidence of late complications in the long-term follow-up population. In 2013, Radium-223 was granted FDA and EMA marketing authorization for the treatment of docetaxel-resistant mCRPC patients.

There are numerous phase III studies ongoing to assess combinations of radium-223 with new anti-androgens, immunotherapy and other drugs. The final results of any of them have not been published yet, but an interesting observation has been published by the team conducting the ERA223 study. This study recruited mCRPC patients with at least two symptomatic skeletal metastases. Participants were not allowed to have visceral metastases or to receive prior docetaxel, radium-223, or abiraterone. All patients enrolled in the study received abiraterone in combination with prednisone and were randomized in a 1: 1 ratio to the Radium-223 arm or placebo. The study did not meet the primary endpoint (time to SRE). The median time to SRE was shorter in the radium-223 arm (22.3 months) compared to the placebo arm (26.0 months) — HR 1.122 (95% CI: 0.917–1.374; p = 0.2636). Secondary endpoints also indicated an adverse effect of the combination of radium and abiraterone. Based on retro-

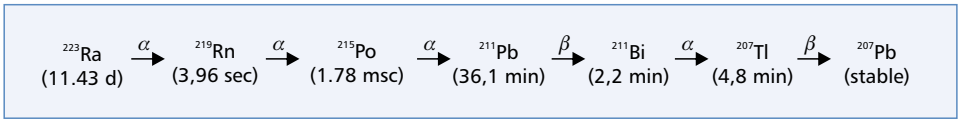

Figure 4. Radium-223 decay chain. Types of decay above the arrows, half-lives in brackets

spective analyses, it was hypothesized that the adverse therapeutic effect was associated with the lower use of bone turnover modulators in the Radium-223 arm compared to placebo. However, while pending further clarification of this finding, the EMA and the FDA have issued warning notices regarding simultaneous use of abiraterone and radium-223.

Immunotherapy

In the middle of the first decade of the 21st century, the American company Dendreon introduced a dendritic vaccine — sipuleucel-T. This medicinal product consists of autologous peripheral blood mononuclear cells (including dendritic cells) incubated with a recombinant antigen resulting from the fusion of the prostate acid phosphatase gene with the granulocyte colony-stimulating factor (G-CSF) gene. In 2006, Eric Small et al. [34] published in the *JCO* the results of phase III D9901 study, which compared sipuleucel-T (administered every 2 weeks) with placebo. The study recruited patients with asymptomatic mCRPC with a baseline Gleason score ≤ 6. The primary endpoint was time to progression (TTP) radiological or clinical (pain or SRE). Patients who progressed in the placebo arm could receive sipuleucel-T. The study did not meet its primary endpoint: the HR for progression-free survival was 1.45 (95% CI: 0.99–2.11; p = 0.052), with a median TTP of 11.7 weeks (vaccine) *vs.* 10.0 weeks (placebo). However, there was a significantly higher risk of death in the placebo arm (HR = 1.70 95% CI: 1.13–2.56; p = 0.01), with a median OS of 25.9 months (sipuleucel-T) *vs.* 21.4 months (placebo). The benefit in terms of OS was maintained in the multivariate analysis, however, the D9901 study was not designed to show a difference in overall survival [30]. In another phase III IMPACT study, the primary endpoint was OS. In the years 2003–2007, overall 512 mCRPC patients were enrolled in this study, regardless of the initial grade or symptoms intensity. Patients were randomized in a 2:1 ratio to either the vaccine or placebo arm. In 2010, Philip Kantoff et al. [35] published in the *NEJM* the results indicating a significantly higher risk of death in the placebo arm (HR = 1.78; 95% CI: 0.61–0.98; p = 0.03) with a median OS of 25.8 months (vaccine) *vs.* 21.7 months (placebo). The benefit of immunotherapy was reaffirmed in a multivariate analysis. Again, no significant differences were found in progression-free survival, which, as we know today, is typical for drugs stimulating specific, cellular antitumor response.

Although antibodies targeting immune checkpoints (CTLA4 as well as PD-1 and PD-L1) have been registered in over 60 indications since 2011, they have not yet been used in prostate cancer. Ipilimumab (an anti-CTLA4 antibody) showed promising activity in phase II trials, however, in a phase III study, no improvement in the prognosis of mCRPC patients was shown [36, 37]. Pembrolizumab, nivolumab (anti-PD-1) and atezolizumab (anti-PD-L1) showed varying degrees of activity in Phase I and II trials, and all of these ICIs are currently being intensively studied in this indication. The results of the studies conducted so far favour combinations rather than monotherapy. However, none of the phase III studies conducted so far has shown a significant improvement in the prognosis of patients after the use of immune checkpoint inhibitors. The main reasons for this include low tumour immunogenicity and the immunosuppressive effect of its stroma.

In November 2019, Emmanuel Antonarakis et al. [38] published in the *JCO* the results of a multi-cohort phase II Keynote-199 study. The study recruited mCRPC patients who received 2–3 lines of prior systemic treatment containing docetaxel and a new generation anti-androgen. In 2016–2017, overall 133 patients with measurable disease showing PD-L1 expression were included in cohort 1, 133 patients with measurable disease but no PD-L1 expression to cohort 2, and 59 patients with the predominance of bone lesions, regardless of PD-L1 expression to cohort 3. All patients received pembrolizumab (200 mg IV q3w up to a maximum of 35 cycles). The primary endpoint was the ORR in cohorts 1 and 2 (RECIST 1.1). ORR in patients with the measurable disease according to RECIST 1.1 criteria (cohorts 1 and 2) was 5%, with complete responses in two patients in cohort 1. The disease control rate in all cohorts according to RECIST 1.1 criteria was 12%, the highest (22%) in cohort 3. The biochemical response rate (PSA decrease by more than 50%) in the entire study population was 6%. Responses were durable: the median duration of response in the overall population was 16.8 months (the highest in cohort 1 — median not reached). Median rPFS was 2.1 months; 2.1 months and 3.7 months, and median OS: 9.5 months (95% CI 6.4–11.9 months); 7.9 months (95% CI 5.9–10.2 months) and 14.1 months (95% CI 10.8–17.6 months) in cohorts 1, 2, and 3, respectively.

Cabozantinib is a pleiotropic multi-kinase inhibitor with anti-angiogenic, anti-proliferative and anti-resorptive effects. It seems to be a promising partner for immunotherapy because inhibiting TAM, MET and AXL kinases improves antigen presentation and T lymphocytes *in vitro* effector functions. It is also known that blocking VEGF-dependent neoangiogenesis facilitates chemotaxis of lymphocytes and their infiltration of the tumour microenvironment [39]. In May 2020, during the ASCO virtual congress, Neeraj Agarwal et al. [40] presented the results of the multi-centre phase I/II COSMIC 021 study, which assessed the activity of atezolizumab (1200 mg IV q3w) combined with cabozantinib

(40 mg qd) in treatment of patients with advanced solid tumours. The primary endpoint of the study was ORR. The presented cohort included 44 mCRPC patients in good performance status (ECOG 0-1), with disease progression in soft tissues on enzalutamide or abiraterone. Patients did not previously receive cabozantinib, immunotherapy or chemotherapy (except for docetaxel used in the stage of castration sensitivity). Most of the patients had visceral or extra-regional lymph nodes metastases. Half of the patients previously received both abiraterone and enzalutamide, and 27% of the patients previously received docetaxel. The objective response rate in the study population was 32%, including 6.8% of complete responses. The disease control rate was 80%. The median duration of response was 8.6 months. The toxicity profile was predictable: 59% of patients experienced grade 3 and 4 toxicities, and 9% of immuno-related adverse events. The combination is currently being evaluated in a phase III study.

PARP inhibitors

Inactivating mutations in genes with known DNA repair function based on homologous recombinational repair mechanism (HRR) have long been studied in the context of their effect on carcinogenesis. These studies, however, were initially limited to cancers characteristic for multiple neoplasia syndromes associated with hereditary, germinal *BRCA1* and *BRCA2* genes mutations (mainly ovarian and breast cancers). Other neoplasms characterized by a high frequency of HRR genes alterations, both germinal and somatic, have been identified relatively recently. Up to 10% of prostate cancers are associated with an inherited *BRCA1* and *BRCA2* genes mutations, however, the latest studies indicate that the percentage of somatic mutations in all HRR genes in prostate cancer is much higher — they were identified in up to 25% of metastases. The *BRCA2* gene mutation is an independent, unfavourable prognostic factor in patients with prostate cancer, and the prognostic significance of other HRR defects is not fully known yet [41].

Simultaneous impairment of homologous recombination and DNA single-strand break repair (SSBR) processes by base excision repair (BER) leads to progressive degradation of DNA and cell death. Stimulation of BER mechanisms activity is one of the functions of enzymes from the group of poly-ADP-ribose polymerases (PARP). Physiologically, PARP binds to a single-stranded DNA damage site and mediates subsequent binding of the repair enzyme complex. Then, during the repair process itself, PARP must unbind from the DNA. PARP inhibitors (PARPi) not only impair the recruitment of a free repair complex but also stabilize the binding of PARP to DNA. Since the stable PARP-DNA complex is an obstacle to the DNA polymerase complex, PARP inhibitors not only prevent damage repair with the use of the BER mechanism but also prevent replication. In a cell with properly functioning other repair mechanisms, such a region will be completely excised, and the resulting double-strand break will be repaired by synthesizing the missing fragment similar to the same region of the sister chromatid (homologous recombination). In HRR defective cells, PARPi cause permanent, lethal damage to the genome.

At the ESMO 2018 Annual Meeting, Wassim Abida et al. [42, 43] presented the preliminary results of a single-armed phase 2 TRITON-2 study, evaluating the activity of PARPi, rucaparib in the treatment of patients with multi-line resistant metastatic prostate cancer and inactivating *BRCA1*, *BRCA2* or *ATM* genes mutations. The study recruited patients with mCRPC who previously received 1 line of docetaxel-based chemotherapy and 1–2 lines of next-generation anti-androgen therapy. The co-primary endpoints were ORR rate, both radiological and PSA.

Out of 25 patients with *BRCA* mutations, as many as 11 (44%) achieved a partial response, and another 9 (36%) achieved disease stabilization. In 5 patients with the *ATM* mutation, no objective responses were observed, but 4 patients (80%) achieved disease stabilization. The safety profile was predictable and 15.3% of patients experienced severe anaemia. The incidence of other serious adverse reactions was < 5%. Based on the results of the TRITON-2 study FDA granted accelerated approval to rucaparib.

In April 2020, Johann de Bono et al. [44] published in the "NEJM" the results of the phase III PROFOUND study. The study recruited mCRPC patients after failure of either abiraterone or enzalutamide-based hormone therapy. Previous chemotherapy with docetaxel was also allowed. The inclusion criterion was the presence in the tumour cells of at least one mutation of the HRR genes: *BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*. HRR genes alterations were identified in 778 patients (28% examined), 387 of whom met the inclusion criteria. Patients were included in two cohorts: A — 245 patients with *BRCA1*, *BRCA2*, *ATM* mutations; B — 142 patients with alteration in other genes. Patients in both cohorts were randomized in a 2:1 ratio to olaparib (300 mg bid) or treatment with a new anti-androgen: abiraterone (1000 mg/d) or enzalutamide (160 mg/d). The primary endpoint was rPFS in cohort A. Secondary endpoints were: OS, radiological, biochemical and cytometric response rates (defined as a decrease in circulating tumour cells from ≥ 5/7.5 mL to < 5/7.5 mL).

The study met its primary endpoint. In cohort A, median rPFS was significantly different in favour of olaparib: 7.4 months *vs.* 3.6 months (HR = 0.34; 95% CI, 0.25–0.47; p < 0.001), in the entire study pop-

ulation the difference in median rPFS was smaller, but still significant: 5.8 months *vs.* 3.5 months, respectively (HR = 0.49; 95% CI; 0.38–0.63; p < 0.001). The use of olaparib was associated with a significant increase in ORR in cohort A: 33% *vs.* 2% (OR 20.86; 95% CI, 4.18–379.18; p < 0.001), and in the entire population: 22% *vs.* 4% (OR 5.93; 95% CI; 2.01–25.4). In interim analysis (for data maturity approximately 40%), median OS in cohort A was 18.5 months *vs.* 15.1 months (HR = 0.64; 95% CI, 0.43–0.97; p = 0.02), and in the entire population 17.5 months *vs.* 14.3 months (HR = 0.67; 95% CI; 0.49–0.93). Significant differences in OS were observed even though approximately 80% of patients in the control arm received olaparib after progression. Adverse events were more frequent in the PARP inhibitor arm: grade 1–4 AEs were reported in 95% and 88% of patients, and grade ≥ 3, in 51% *vs.* 38% patients in the PARPi and placebo arm, respectively. The most common AEs in the active treatment arm included anaemia, nausea, and fatigue/asthenia, whilst in the control arm there was fatigue/asthenia. One side effect-related death was noted in each study arm. Based on the results of the PROFOUND study, olaparib was approved by the FDA and EMA for the treatment of mCRPC patients after the failure of modern hormone therapy. In the US, the drug is used in patients with germinal or somatic mutations in the HRR genes, and in Europe only in patients with germinal or somatic *BRCA1* or *BRCA2* genes mutations.

The remaining PARPi: niraparib and talazoparib, showed promising activity in the dHRR population in phase II studies and are currently being evaluated in randomized trials [45].

Summary

Systemic treatment is evolving towards strategies that are increasingly selective for tumour tissue and at the same time more personalized. A better understanding of the mechanisms responsible for prostate cancer carcinogenesis has resulted in an unprecedented rate of new therapeutic options emergence in the last two decades. The reliability of AR-dependent signalling pathways blocking, offered by new molecules, has resulted in an extension of the period measured in years in which patients can be offered active therapies, not adversely affecting the quality of life. Advances in nuclear medicine resulted in the development of sensitive radiotracers as well as therapeutic isotopes which prolong overall survival. Research on the role of HRR allowed patients with other types of cancer to take advantage of the PARPi activity.

However, there are still many challenges. The use of new generation antiandrogens is associated with a more frequent occurrence of cancers completely independent of androgen signalling, showing small-cell or neuroendocrine features. The incidence of prostate cancer is also increasing in relatively young patients who need much more aggressive and long-acting therapeutic strategies. The new therapies generate a considerable strain on the healthcare system finances. Finally, treatment personalization itself contributes to the atomization of therapeutic algorithms, makes it difficult to qualify patients for clinical trials, forcing an even narrower sub-specialization and greater expenditure of time spent on lifelong learning. At the beginning of the third decade of the 21st century, we will have to overcome these problems.

Conflict of interest

Paweł Potocki received honoraria and travel grants from Astellas, Astra Zeneca, Bayer, Janssen, MSD, Merck, Roche.

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References

1. Adams J. The case of scirrhous of the prostate gland with corresponding affliction of the lymphatic glands in the lumbar region and in the pelvis. Lancet. 1853; 1(1): 393.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424, doi: 10.3322/caac.21492, indexed in Pubmed: 30207593.
3. White JW. II. The Present Position of the Surgery of the Hypertrophied Prostate. Ann Surg. 1893; 18(2): 152–188, doi: 10.1097/00000658-189307000-00020, indexed in Pubmed: 17859954.
4. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972; 22(4): 232–240, doi: 10.3322/canjclin.22.4.232, indexed in Pubmed: 4625049.
5. Mainwaring WI. A soluble androgen receptor in the cytoplasm of the male mastomys prostate. Urol Res. 1978; 6(1): 29–33, doi: 10.1007/BF00257079, indexed in Pubmed: 644728.
6. Schally AV, Kastin AJ, Arimura A. Hypothalamic follicle-stimulating hormone (FSH) and luteinizing hormone (LH)-regulating hormone: structure, physiology, and clinical studies. Fertil Steril. 1971; 22(11): 703–721.
7. Messner EA, Steele TM, Tsamouri MM, et al. The androgen receptor in prostate cancer: Effect of structure, ligands and spliced variants on therapy. Biomedicines. 2020; 8(10), doi: 10.3390/biomedicines8100422, indexed in Pubmed: 33076388.
8. Thadani-Mulero M, Nanus DM, Giannakakou P. Androgen receptor on the move: boarding the microtubule expressway to the nucleus. Cancer Res. 2012; 72(18): 4611–4615, doi: 10.1158/0008-5472.CAN-12-0783, indexed in Pubmed: 22987486.
9. Seruga B, Ocana A, Tannock IF. Drug resistance in metastatic castration-resistant prostate cancer. Nat Rev Clin Oncol. 2011; 8(1): 12–23, doi: 10.1038/nrclinonc.2010.136, indexed in Pubmed: 20859283.
10. Ringel I, Horwitz SB. Studies with RP 56976 (taxotere): a semisynthetic analogue of taxol. J Natl Cancer Inst. 1991; 83(4): 288–291, doi: 10.1093/jnci/83.4.288, indexed in Pubmed: 1671606.
11. Bai S, Zhang BY, Dong Y. Impact of taxanes on androgen receptor signaling. Asian J Androl. 2019; 21(3): 249–252, doi: 10.4103/aja.aja_37_18, indexed in Pubmed: 29900882.

12. Tannock I, Wit Rde, Berry W, et al. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. New England Journal of Medicine. 2004; 351(15): 1502–1512, doi: 10.1056/nejmoa040720.
13. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol. 2008; 26(2): 242–245, doi: 10.1200/JCO.2007.12.4008, indexed in Pubmed: 18182665.
14. Mita AC, Denis LJ, Rowinsky EK, et al. Phase I and pharmacokinetic study of XRP6258 (RPR 116258A), a novel taxane, administered as a 1-hour infusion every 3 weeks in patients with advanced solid tumors. Clin Cancer Res. 2009; 15(2): 723–730, doi: 10.1158/1078-0432.CCR-08-0596, indexed in Pubmed: 19147780.
15. Bono Jde, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. The Lancet. 2010; 376(9747): 1147–1154, doi: 10.1016/s0140-6736(10)61389-x.
16. de Wit R, de Bono J, Sternberg CN, et al. CARD Investigators. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019; 381(26): 2506–2518, doi: 10.1056/NEJMoa1911206, indexed in Pubmed: 31566937.
17. Cabazitaxel versus the switch to alternative ar-targeted agent (enzalutamide or abiraterone) in metastatic castration-resistant prostatę cancer (mCRPC) patients previously treated with docetaxel and who rapidly failed a prior ar-targeted agent (CARD), https://clinicaltrials.gov/ct2/show/NCT02485691 (26.01.2021).
18. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368: 138–148, doi: 10.1056/NEJMoa1209096.
19. Ryan CJ, Smith MR, Fizazi K, et al., "Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015; 16 (2): 152–160P. doi: 10.1016/S1470-2045(14)71205-7.
20. Fizazi K, Scher H, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. The Lancet Oncology. 2012; 13(10): 983–992, doi: 10.1016/s1470-2045(12)70379-0.
21. Ryan C, Smith MR, Fizazi K, et al. Final Overall survival analysis of COU-AA-302, a randomized phase 3 study of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy. ESMO 2014; Abstract 7530 (oral presentation).
22. Attard G, Borre M, Gurney H, et al. PLATO collaborators. Abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. J Clin Oncol. 2018; 36(25): 2639–2646, doi: 10.1200/JCO.2018.77.9827, indexed in Pubmed: 30028657.
23. Morris M, Heller G, Bryce A, et al. Alliance A031201: A phase III trial of enzalutamide (ENZ) versus enzalutamide, abiraterone, and prednisone (ENZ/AAP) for metastatic castration resistant prostate cancer (mCRPC). Journal of Clinical Oncology. 2019; 37(15_suppl): 5008–5008, doi: 10.1200/jco.2019.37.15_suppl.5008.
24. Scher HI, Fizazi K, Saad F, et al. AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012; 367(13): 1187–1197, doi: 10.1056/NEJMoa1207506, indexed in Pubmed: 22894553.
25. Beer TM, Armstrong AJ, Rathkopf DE, et al. PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014; 371(5): 424–433, doi: 10.1056/NEJMoa1405095, indexed in Pubmed: 24881730.
26. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL Study. Eur Urol. 2017; 71(2): 151–154, doi: 10.1016/j.eururo.2016.07.032, indexed in Pubmed: 27477525.
27. Smith MR, Antonarakis ES, Ryan CJ, et al. Phase 2 Study of the Safety and Antitumor Activity of Apalutamide (ARN-509), a Potent Androgen Receptor Antagonist, in the High-risk Nonmetastatic Castration-resistant Prostate Cancer Cohort. Eur Urol. 2016; 70(6): 963–970, doi: 10.1016/j.eururo.2016.04.023, indexed in Pubmed: 27160947.
28. Fizazi K, Massard C, Bono P, et al. Safety and Antitumour Activity of ODM-201 (BAY-1841788) in Castration-resistant, CYP17 Inhibitor-naïve Prostate Cancer: Results from Extended Follow-up of the ARADES Trial. Eur Urol Focus. 2017; 3(6): 606–614, doi: 10.1016/j.euf.2017.01.010, indexed in Pubmed: 28753849.
29. Sgouros G, Hobbs R, Josefsson A. Dosimetry and Radiobiology of Alpha-Particle Emitting Radionuclides. Curr Radiopharm. 2018; 11(3): 209–214, doi: 10.2174/1874471011666180426130058, indexed in Pubmed: 29697036.
30. Godlewski T. A new radio-active product from actinium. Nature. 1905; 71(1839): 294–295, doi: 10.1038/071294b0.
31. Morris MJ, Corey E, Guise TA, et al. Radium-223 mechanism of action: implications for use in treatment combinations. Nat Rev Urol. 2019; 16(12): 745–756, doi: 10.1038/s41585-019-0251-x, indexed in Pubmed: 31712765.
32. Parker C, Nilsson S, Heinrich D, et al. ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013; 369(3): 213–223, doi: 10.1056/NEJMoa1213755, indexed in Pubmed: 23863050.
33. Parker CC, Coleman RE, Sartor O, et al. Three-year Safety of Radium-223 Dichloride in Patients with Castration-resistant Prostate Cancer and Symptomatic Bone Metastases from Phase 3 Randomized Alpharadin in Symptomatic Prostate Cancer Trial. Eur Urol. 2018; 73(3): 427–435, doi: 10.1016/j.eururo.2017.06.021, indexed in Pubmed: 28705540.
34. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol. 2006; 24(19): 3089–3094, doi: 10.1200/JCO.2005.04.5252, indexed in Pubmed: 16809734.
35. Kantoff PW, Higano CS, Shore ND, et al. IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010; 363(5): 411–422, doi: 10.1056/NEJMoa1001294, indexed in Pubmed: 20818862.
36. Beer TM, Kwon ED, Drake CG, et al. Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer. J Clin Oncol. 2017; 35(1): 40–47, doi: 10.1200/JCO.2016.69.1584, indexed in Pubmed: 28034081.
37. Kwon ED, Drake CG, Scher HI. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014; 15(7): 700–712, doi: 10.1016/S1470-2045(14)70189-5.
38. Antonarakis E, Piulats J, Gross-Goupil M, et al. Pembrolizumab for Treatment-Refractory Metastatic Castration-Resistant Prostate Cancer: Multicohort, Open-Label Phase II KEYNOTE-199 Study. J Clin Oncol. 2020; 38(5): 395–405, doi: 10.1200/jco.19.01638.
39. Bergerot P, Lamb P, Wang E, et al. Cabozantinib in Combination with Immunotherapy for Advanced Renal Cell Carcinoma and Urothelial Carcinoma: Rationale and Clinical Evidence. Mol Cancer Ther. 2019; 18(12): 2185–2193, doi: 10.1158/1535-7163.MCT-18-1399, indexed in Pubmed: 31792125.
40. Agarwal N, Loriot Y, McGregor B, et al. Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer: Results of cohort 6 of the COSMIC-021 study. J Clin Oncol. 2020; 38(15_suppl): 5564–5564, doi: 10.1200/jco.2020.38.15_suppl.5564.
41. Armenia J, Wankowicz SAM, Liu D, et al. PCF/SU2C International Prostate Cancer Dream Team. The long tail of oncogenic drivers in prostate cancer. Nat Genet. 2018; 50(5): 645–651, doi: 10.1038/s41588-018-0078-z, indexed in Pubmed: 29610475.
42. Abida W, Bryce AH, Vogelzang NJ, et al. 793PDPreliminary results from TRITON2: A phase II study of rucaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations. Ann. Oncol., 2018; 29 (suppl_8): 2018P. doi: 10.1093/annonc/mdy284.002.
43. Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration abstract. 2020; 2P doi: 10.1200/JCO.20.01035.
44. Bono Jde, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM. 2020; 382(22): 2091–2102, doi: 10.1056/nejmoa1911440.
45. Smith M, Sandhu S, Kelly W, et al. Phase II study of niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD): Preliminary results of GALAHAD. J Clin Oncol. 2019; 37(7_suppl): 202–202, doi: 10.1200/jco.2019.37.7_suppl.202.