

## DEVELOPMENTS IN PROSTATE CANCER THERAPY: FROM THE ANDROGEN RECEPTOR TO ANTIANDROGENS AND BEYOND

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### Abstract

Prostate cancer is the second most common malignancy in men. The androgenic receptor (AR) is the main therapeutic target for this type of cancer, hormone therapy being the cornerstone of patient management, despite resistance developing over time in some cases. The scientific concern and practical necessity for more effective therapies have led to the introduction of novel drug classes, including new taxanes, PARP inhibitors and immunotherapeutic agents. Studies regarding the complex mechanisms of action which account for the therapeutic effects of these drugs are supported by clinical trials which confirm the optimization of survival parameters. The present article summarizes current diagnostic and therapeutic trends in prostate cancer treatment; it is organized in distinct sections aimed at: (i) the evolution of different concepts and approaches in the histopathological classification, (ii) the structure and function of the androgenic receptor and its truncated variant 7, considered a clear indicator of the lack of response to hormone treatment, (iii) the therapeutic principles in both localized and locally advanced prostate cancer, (iv) the innovative strategies in treating castration-resistant and metastatic prostate cancer. Reviewing these recent and complex aspects generates a meaningful insight regarding the advancements in patient-tailored diagnosis and therapy, aimed at individualized treatment that reconciles both the biological profile and the subjective choices of the patient.

### Rezumat

Cancerul de prostată reprezintă a doua cea mai comună neoplazie la bărbați. Receptorul androgenic (RA) reprezintă principala țintă terapeutică, hormonoterapia constituind axul critic al tratamentului – dar unii pacienți dezvoltă însă, în timp, rezistență. Interesul științific pentru dezvoltarea unor terapii mai eficiente a condus la introducerea unor noi clase de medicamente, care includ taxani de generație nouă, inhibitori PARP și agenți imunoterapeutici. Cercetarea mecanismelor de acțiune complexe care stau la baza efectelor terapeutice este susținută prin studii clinice care confirmă optimizarea parametrilor de supraviețuire. Articolul concentrează repere diagnostice și terapeutice actuale operaționale în cancerul de prostată. Parcurgerea informației este facilitată prin organizarea în secțiuni distincte care vizează: (i) evoluția noțiunilor și conceptelor în clasificarea histopatologică, (ii) structura și funcția receptorului androgenic și a variantei 7 trunchiate, considerată indicator absolut al lipsei de răspuns la tratamentul hormonal, (iii) principii terapeutice în cancerul de prostată localizat și local avansat, (iv) strategii inovative în tratamentul cancerului de prostată rezistent la castrare și metastatic. Trecerea în revistă a informației recente permite astfel o imagine de ansamblu a progreselor înregistrate în diagnosticul și terapia centrată pe pacient, în efortul de a stabili un tratament individualizat, concordant cu profilul biologic obiectiv și opțiunile subiective ale acestuia.

**Keywords:** prostate cancer, pathology, androgenic receptor, hormone therapy, therapeutics development

### Introduction

The worldwide incidence rate places prostate cancer as the second most common neoplasm in men [40]. Recent data indicates over 1.3 million newly diagnosed cases, one in seven men being affected. With an annual mortality rate of 360,000 cases, it accounts for approximately 4% of cancer deaths [40]. Patients diagnosed in the early stages reach a 5-year survival

rate of 100%, while for advanced, metastatic stages, the 5-year survival rate drops below 30% [40]. Thus, despite the important advances in treating this cancer, early diagnosis still represents the key to a favourable evolution and life expectancy of the patient.

Due to the specific hormonal profile of the organs from which they originate, prostate cancer, along with breast, ovarian and endometrial cancer, are comprised

in a special category of tumours, namely hormone-dependent cancers [53]. Strictly referring to the prostate, androgens and their receptors are essential in the morphofunctional development, but the hormonal profile may become an intrinsic component in the molecular mechanism of carcinogenesis [53]. A deeper understanding of the hormonal dynamics and molecular changes has led to advances in the development of new targeted therapeutics, including primarily the androgen receptor (AR), but not solely. The use of new types of drugs undoubtedly has positive effects in disease management, reflected in a prolonged progression-free survival (PSF) and overall survival (OS). On the other hand, the side effects worth mentioning include toxicity and the appearance of treatment-refractory forms of the disease with, consequently, increased aggressiveness [53].

The management of a newly diagnosed prostate neoplasm requires the involvement of a multidisciplinary team including several specialties (oncology, pathology, urology, radiology, radiotherapy), depending on the complexity of the case.

### Classification criteria in prostate cancer

Prostate cancer is an eloquent example of the evolution of the criteria applied in morphological classification systems. The system designed by Donald Gleason, used worldwide since the 1960s [23], has been systematically revised, in direct relation to the clinical and prognostic significance [12, 13, 47]. Unlike other systems, the classification of prostate cancer was based on an essential element – the histoarchitectural pattern, which led to the definition of 5 histological grades, marked from 1 to 5 [23]. The sum of the dominant (primary) grade and subdominant (secondary) grade constituted the Gleason score, with values varying between 2 and 10 [23].

Changes of the grading criteria were proposed by Gleason in 1974 and 1977 [12, 24, 25], resulting in grouping the scores into the following categories: 2 - 3, 4 - 5, 6, 7 and 8 - 10, concerning the prognosis. The conference organized by the International Society of Urological Pathology (ISUP) in 2005 [12, 47] also brought amendments to the grading system. Thus, it was established that grade 1 corresponds to adenosis, grade 2 is rarely assigned, grade 3 includes the cribriform pattern with small, uniform glands with a well-defined lumen, grade 4 consists of poorly formed acini and irregular cribriform glands, and grade 5 is characterized by comedonecrosis, and presence of single tumoural cells, solid cords and masses. The conference led to a consensus regarding the classification of all histological variants (except the mucinous ones), based only on the histoarchitectural features, without taking into account the cytological aspects. Another novelty was the decision to consider the presence of the higher grade pattern, even if it represents a minor component

(tertiary grade), and to add it to the most representative grade (primary grade) in calculating the Gleason score [13]. Subsequently, as a result of the changes made in 2005, the Gleason score values comprised between 6 and 10 were distributed into 3 clinical risk classes: low, intermediate and high [12].

In 2014, ISUP Consensus Conference assigned the cribriform and glomeruloid pattern a Gleason grade 4 and decided that the mucinous histopathological variant of adenocarcinoma should be graded exclusively on histoarchitectural features. Also, a new approach in prostate cancer stratification was proposed, by defining 5 prognostic groups, called ISUP grades. Thus, prognostic grade group 1 assimilated Gleason score 3 + 3, grade group 2 corresponded to Gleason score of 3 + 4, grade 3 was assigned for Gleason score 4 + 3, grade 4 for Gleason scores of 8 (4 + 4, 3 + 5, 5 + 3), while grade 5 was equivalent to Gleason scores 9 and 10 [49]. The proposed ISUP grading system is only applicable to needle biopsies; the rule is that a higher tertiary pattern if present, no matter the proportion, should be considered in the grading system as the secondary pattern. For radical prostatectomy, no consensus has yet been established for quantifying a tertiary pattern. All these clarifications increased the quality of the assessment of prostate biopsies, due to a much more objective perspective of the prognosis [12].

### The androgen receptor

AR plays a major role in prostate carcinogenesis, its stimulation promoting tumour proliferation. Therefore, AR is considered the most important therapeutic target [53]. On the other hand, its absence is correlated with a less differentiated, more aggressive tumour phenotype, characterized by accelerated tumour growth and a lack of therapeutic response, resulting in poor prognosis [53].

AR, also known as NR3C4 (subfamily 3, group C, gene 4), belongs to the same family of nuclear receptors as the oestrogen receptor (ER), progesterone receptor, glucocorticoid and mineralocorticoid receptors [51]. This type of receptor is ligand-dependent and by binding to 5 $\alpha$ -dihydrotestosterone and testosterone it initiates and promotes male sexual differentiation and development [35]. The gene encoding AR is placed on the X chromosome, the Xq11-Xq12 locus, being composed of 8 exons and 2757 nucleotides. The size of the introns varies from 0.7 to 2.6 kb. The gene encodes a 110 kDa protein containing 919 amino acids. AR is composed of 3 major functional domains: the amino-terminal domain encoded by the first exon; the DNA binding domain, encoded by exons 2 and 3; the ligand-binding domain, encoded by exons 4 - 8. This protein acts as a transcription factor activated by steroid hormones [35, 51]. Hormone binding takes place in the cytoplasm, the receptor dissociates from

the accessory proteins promoting the translocation into the nucleus, where it dimerizes and initiates the transcription process of androgen responsible genes [11, 56]. The non-genomic mechanism consists of the interaction between androgens and cytoplasmic signalling proteins, leading to rapid changes in ion transportation. These can indirectly cause changes in gene transcription, for example, phosphorylation of other transcription factors [51]. There are 2 isoforms of AR, described as (i) AR-A, with a molecular weight of 87 kDa, characterized by a truncated amino-terminal domain (the first 187 amino acids are missing), due to *in vitro* proteolysis; (ii) AR-B with a molecular weight of 110 kDa and a complete structure [58]. Repetition of CAG nucleotides affects AR function and influences the receptor's sensitivity; the length of the CAG sequence in the AR gene differs with race, variations which correlate with an increased risk for developing prostate cancer [42]. Given the involvement of the AR in different hormonal processes, blocking it plays a critical part in the therapy of hormone-dependent prostate cancer.

#### *Androgen receptor splice variant 7 (AR-V7) and resistance to antiandrogen therapy*

Resistance to antiandrogen treatment occurs over time. One of the most common adaptation mechanisms is the appearance of the androgen receptor splice variant 7 (AR-V7), described relatively recently and considered an absolute indicator of refractory response to antiandrogen therapy. AR-V7 (AR3) is composed of exons 1 - 3, which encode the amino-terminal domain and also the DNA binding domain, with a unique 16 amino acid sequence (16 variant-specific amino acids) at the carboxy-terminal end encoded by a variant-specific cryptic exon 3 (CE3) within intron 3 [44, 45].

This variant is biologically active, but lacks the Ligand Binding Domain (LBD). Due to the lack of this ligand, classical anti-AR therapy (such as abiraterone or enzalutamide) becomes ineffective, this binding domain being indispensable for the drug action [22, 44, 45]. The eligibility criteria for AR-V7 testing (AR-V7 Nucleus Detect Assay) are (i) diagnosis of castration-resistant prostate cancer; (ii) previous ineffective anti-androgen therapy. One of the tests available for assessing the AR-V7 status is Oncotype DX AR-V7 [44, 45]. Oncotype DX AR-V7 testing detects the nuclear-localized AR-V7, not the cytoplasmic one. Nuclear detection of AR-V7 is a valuable biomarker of resistance because although AR-V7 proteins are also present at a cytoplasmic level, the transcription of growth factors occurs only in the nucleus [44, 45].

The number of patients who exhibit AR-V7 increases with exposure to anti-AR therapy. According to the available published data [4, 44, 45], 1 in 5 patients (18%) is AR-V7 positive following abiraterone or enzalutamide therapy, and 1 out of 3 patients (31%) is AR-V7 positive following two lines of antiandrogen

therapy, while hormone naive prostate cancer patients are found positive in only 3% of cases.

Consequently, recent data support the need for AR-V7 testing for patients with castration-resistant metastatic prostate cancer for better guidance of the therapy. In their case, maintaining the hormone therapy does not seem to bring benefits. The optimal therapeutic decision is either taxane-based chemotherapy [4], which significantly reduces the death rate (by 76%), or newer methods of treatment, such as PARP inhibitors, which constitute more efficient alternatives [10, 46].

#### **Treatment of localized and locally advanced prostate cancer**

##### *Risk groups*

The suspicion of prostate cancer requires confirmation by histopathological examination of a prostate needle biopsy sample. The therapeutic strategy for this hormone-dependent neoplasm includes surgery, radiation therapy and hormone therapy, and the patient's options are decided based on the inclusion in a risk group. The European Society for Medical Oncology (ESMO) guide defines 3 major prognostic groups: low-risk, intermediate-risk and high-risk [38], while the National Comprehensive Cancer Network (NCCN) guide provides additional prognostic groups, defined as very low, low, favourable intermediate, unfavourable intermediate, high and very high-risk, respectively [34, 43]. The inclusion in these risk groups is based on the following parameters: clinical staging, Gleason score and value of Prostate-Specific Antigen (PSA). The risk groups according to NCCN are the following: (i) very low-risk – meeting all of the following conditions: T1c, grading group 1, PSA < 10 ng/mL, less than 3 biopsy cores with ≤ 50% tumour extent and PSA density < 0.15 ng/mL/g; (ii) low-risk – which does not fall into the very low-risk group and satisfies all of the following conditions: T1-T2a, grading group 1, PSA < 10 ng/mL; (iii) intermediate-risk – T2b-T2c, grading group 2 or 3, PSA 10 - 20 ng/mL; this group is subdivided into favourable intermediate (when it meets one of the criteria of the intermediate risk group, grading group 1 or 2, ≤ 50% tumour extent on the biopsy) and unfavourable intermediate (when it complies with 2 or 3 criteria of the group, grading group 3, and ≥ 50% tumour extent on the biopsy sample); (iv) high-risk – T3a or grading group 4 or 5, PSA > 20 ng/mL; (v) very high-risk – comprises one of the following conditions: T3b-T4, primary Gleason pattern 5, 2 or 3 high-risk criteria, more than 4 biopsy cores with grading group 4 or 5 [43].

The therapeutic decision is established according to the patient's choice after he is presented with the alternating potential benefits and adverse effects – that include, but are not limited to: sexual dysfunction, infertility, urination and bowel motility changes, peripheral neuropathy [3, 26, 33]. The patient may

prefer, in localized low- or intermediate-risk disease, for active surveillance, which involves follow-up of the case by periodic prostate biopsy, PSA monitoring and magnetic resonance imaging (MRI). Last but not least, treatment options must take into account the life expectancy of each patient, as prostate cancer generally occurs in elderly patients. It should be noticed that more cases are diagnosed in younger patients, especially in the context of family history of cancer [34, 43].

#### *Principles of hormone therapy*

Most prostate cancers are hormone-sensitive at the time of diagnosis. Based on the historical observation that eunuchs were not affected by this disease, it was assumed that a surgical castration would stop the progression of prostate cancer. Later, other castration methods became available, like endocrine treatment. Hormone therapy is used in all stages of the disease – except for very low and low-risk groups, most often in combination with other therapies, and represents the backbone of the prostate treatment plan [34, 43]. In the 21<sup>st</sup> century, patient castration is performed using two classes of drugs (also known as androgen deprivation therapy): luteinizing hormone-releasing hormone (LHRH) agonists and antagonists [34, 43]. The LHRH agonists used are goserelin (Zoladex<sup>®</sup>, AstraZeneca, United Kingdom), histrelin (Vantas<sup>®</sup>, Endo Pharmaceuticals Inc., USA), leuprolide (Eligard<sup>®</sup>, Angelini Pharma, Italy) and triptorelin (Decapeptyl<sup>®</sup>, Ipsen Limited, France). The action mechanism of agonists consists of binding to the gonadotropin-releasing-hormone (GnRH) receptor and internalizing it, while having an almost complete bioavailability, with a plasma peak of approximately 2 hours. GnRH receptors are located in the pituitary gland and by binding to them; there is initially a release of luteinizing hormone (LH) and thus an increase of male sex hormones lasting for about 14 days. After 14 - 21 days, through a negative feedback mechanism, there is a decrease of sex hormones to levels similar or sometimes even below the ones reached after surgical castration.

In order to regulate the initial increase of LH levels – a phenomenon called “flare-up”, first-generation AR antagonists can be added, such as bicalutamide (Casodex<sup>®</sup>, AstraZeneca, UK), nilutamide (Nilandron<sup>®</sup>, Concordia Pharmaceuticals Inc., UK) and flutamide (Eulexin<sup>®</sup>, Schering-Plough, USA). These second-class drugs are antiandrogens that competitively block the AR – biological target of testosterone and dihydro-testosterone.

The third class of drugs used in the chemical castration of the patient is represented by LHRH antagonists, for example, degarelix (Firmagon<sup>®</sup>, Ferring Pharmaceuticals, Switzerland) which acts by competitively binding to GnRH receptors, leading to a decrease in LH and implicitly testosterone, without the initial flare-up phenomenon observed in LHRH agonists, so the

association with antiandrogens (e.g. bicalutamide) is no longer necessary [34, 43].

#### *Principles of surgery and radiotherapy*

Classical or robotic surgical treatment aims to achieve complete removal of prostate tissue and seminal vesicles while preserving sphincter and sexual functions. Curative treatment includes, in addition to surgery, radiotherapy (external or brachytherapy) and local tissue ablation procedures (cryoablation or high intensity focused ultrasound – HIFU) [34, 38, 43].

The effectiveness of radiation therapy has been demonstrated by studies conducted by the Scandinavian Prostate Cancer Group (SPCG-7/SFUO-3) [57] and the National Cancer Institute of Canada/Medical Research Council (NCIC/MRC) [55]. The Canadian trial showed an increase in 7-year survival from 66% to 74%, following the addition of radiation therapy to androgen deprivation treatment [55]. The principle of radiotherapy is to alter the tumour cell DNA. External radiotherapy is administered over a longer time, according to a therapeutic plan, to obtain optimal results and at the same time allowing the recovery of normal tissues exposed to treatment [16].

In locally advanced disease, especially when an upfront radical prostatectomy is no longer an option given the large tumour volume, and external radiation therapy has multiple side effects that outweigh the benefits of treatment, neoadjuvant hormone therapy can be used, followed by imaging reassessment and, in the case of a good response, definitive radiotherapy. In selected cases, radical prostatectomy and pelvic lymphadenectomy may be indicated. A particular situation is the high-risk localized prostate cancer in young men with good performance status – when international guidelines recommend neoadjuvant chemotherapy with docetaxel [38].

#### **Treatment in metastatic castration-resistant prostate cancer**

Castration-resistant prostate cancer is the condition in which the disease progresses during androgen deprivation therapy, while the serum testosterone is under castration level [8]. Castration resistance is achieved through AR gene alteration, transcriptional compensation, alternative steroid receptors, mutation, or copy number alterations of genes encoding AR co-regulators [28].

Overcoming this resistance is possible in some cases with the addition of novel hormone therapies which include new antiandrogen agents such as CYP17 inhibitors (abiraterone – Zytiga<sup>®</sup>, Janssen-Cilag, Italy) and second-generation antiandrogens (enzalutamide – Xtandi<sup>®</sup>, Astellas Pharma, Japan, apalutamide – Erleada<sup>®</sup>, Janssen-Cilag, Italy and darolutamide – Nubeqa<sup>®</sup>, Bayer HealthCare, Germany) [38].

Abiraterone in combination with prednisone increased OS – a result confirmed in two international phase

III clinical trials, LATITUDE and STAMPEDE [19, 20, 31]. Abiraterone selectively inhibits the enzyme 17 $\alpha$ -hydroxylase/C17,20-lyase (CYP17) – present in the testis, adrenal glands and prostate and necessary for the biosynthesis of androgen hormones. CYP17 catalyses the conversion of pregnenolone and progesterone to testosterone precursors, dehydroepiandrosterone and androstenedione, by 17 $\alpha$ -hydroxylation and cleavage of the C17,20 bond [15, 52].

Another example of therapeutic success by blocking the activity of AR is enzalutamide – a potent signalling inhibitor in AR, which interferes with different steps in the signalling pathway by (i) competitively inhibiting the binding of androgen hormones to AR; (ii) inhibition of nuclear translocation of activated receptors; (iii) suppression of the association between activated AR and DNA, even in the context of AR overexpression in tumour cells of antiandrogen-resistant prostate cancer. Thus, enzalutamide treatment inhibits tumour cell proliferation, induces cell death and tumour regression [6].

Two phase III trials, ARCHES (which enrolled patients presenting tumour progression consecutive to docetaxel administration) [5], followed by ENZAMET (with chemotherapy-naïve patients, sensitive to castration) [9], have studied the benefits of enzalutamide in metastatic prostate cancer. In the randomized, open-label, phase III ENZAMET trial, the group of patients who underwent chemical castration and received enzalutamide was compared with a control group of chemically castrated patients who received other antiandrogens such as bicalutamide, flutamide or nilutamide, with a significant improvement in OS [9]. In the multinational, double-blind, randomized, placebo-

controlled, phase III ARCHES study, enzalutamide therapy substantially improved PFS [5].

The multicentre, randomized, double-blind, placebo-controlled, phase III SPARTAN study demonstrated the effectiveness of apalutamide in increasing metastasis-free survival [48]. This non-steroidal antiandrogenic compound is a selective and competitive AR antagonist, structurally similar to enzalutamide. It has a higher affinity for AR than bicalutamide, but the acquired mutation F876L, identified in prostate cancer, leads to treatment resistance to both enzalutamide and apalutamide [48]. Apalutamide also proved its efficiency in the multicentre, randomized, double-blind, placebo-controlled, phase III TITAN study, by its impact on OS, the only uncertainty being the effectiveness when it is used after docetaxel, as only 11% of 1052 enrolled patients were pre-treated with this drug [7].

A new agent, darolutamide, also useful for patients with the F876L mutation, acts additionally as a silent antagonist of PR, with an antagonistic effect on AR. Its efficacy was validated by the multinational, randomized, double-blind, placebo-controlled, phase III ARAMIS trial [18].

In metastatic disease, treatment options include, besides androgen deprivation (less often surgical castration), first and second-generation antiandrogens and radiotherapy in oligometastatic disease, agents used to prevent the loss of bone density, such as bisphosphonates or denosumab and Radium-223 in patients with bone lesions, chemotherapy drugs like docetaxel and cabazitaxel and, last but not least, personalized medicine [27, 38] (Figure 1).

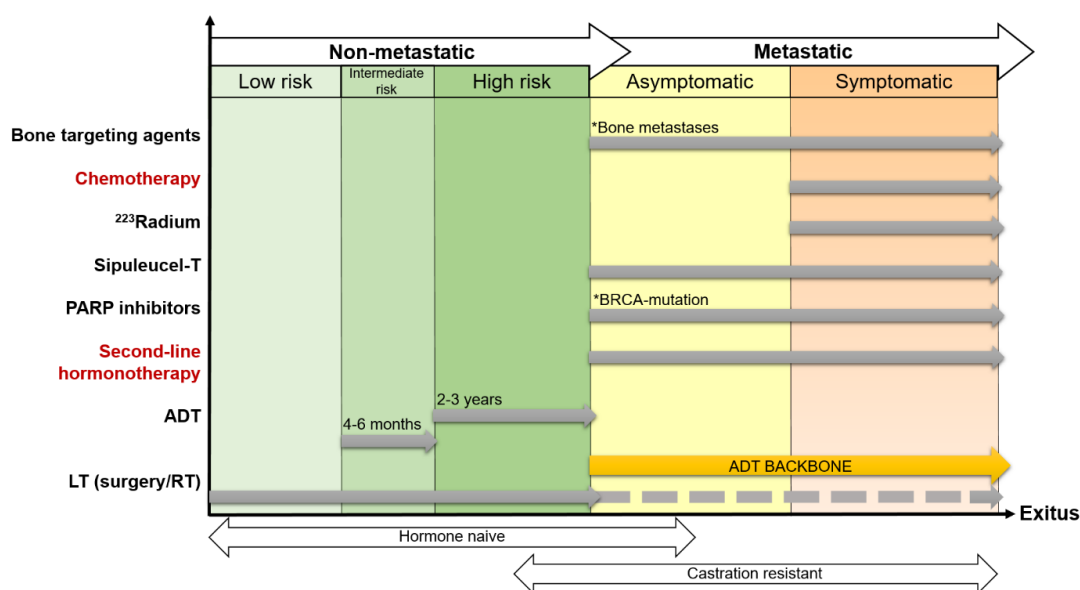


Figure 1.

Treatment options in prostate cancer (PARP – poly ADP ribose polymerase, ADT – androgen deprivation therapy, LT – local therapy, RT – radiotherapy), (Note: exceptions may apply)

Regarding chemotherapy, two taxane drugs, docetaxel and, more recently, cabazitaxel (Jevtana<sup>®</sup>, Sanofi-Aventis, France) are used to treat castration-resistant and metastatic prostate cancer. Cabazitaxel is generally used after disease progression under docetaxel treatment [37]. The FIRSTANA multi-centre, randomized, open-label study, which compared the efficacy of cabazitaxel *versus* docetaxel as first-line chemotherapy agents in prostate cancer, showed a better tumoural response in patients receiving cabazitaxel chemotherapy, but a lower safety profile. However, no increase in OS was observed in the group receiving cabazitaxel compared to the group receiving docetaxel [36].

Taxanes are antineoplastic drugs that act by disorganizing the cell's microtubular network, an essential element in multiplication during mitosis, thus leading to a cell cycle block in the M phase [1]. Compared to antiandrogen drugs, tolerance may be deficient due to side effects associated with treatment, mostly haematological [21] and neurological toxicity [33]. Other chemotherapeutic agents that can be used are mitoxantrone and estramustine, usually when all other agents have failed, including platinum salts [34, 38, 43].

A particular situation is the oligometastatic disease – an entity in which the patient has few metastases, limited to the bone (for example, a maximum of 4 bone metastases, one of them occurring in a different site other than the pelvis or spine). Although there is no consensus regarding the definition of oligometastatic disease or how this should be treated, some guidelines recommend a potentially curative approach, such as hormone therapy associated with prostatic tissue and metastatic sites irradiation; however, none of the studies supporting this recommendation showed any benefit in terms of OS [39].

#### *Immunotherapy*

Currently, sipuleucel-T (Provenge<sup>®</sup>, Dendreon Pharmaceutical, USA) is the only agent approved by the Food and Drug Administration (FDA) and used as an immunotherapeutic drug in treating castration-resistant prostate cancer [41]. Sipuleucel-T represents an innovative approach of cellular immunotherapy in which host lymphocytes are engineered in a cell culture medium to recognize and destroy acid phosphatase-presenting cells.

Antigen-presenting cells are collected from the patient's peripheral blood and subsequently cultured and activated with a recombinant human protein (PAM-GM-CSF) in prostatic acid phosphatase (PAP) medium. Thus, the immune response can be redirected against the PAP, expressed on the surface of prostate cells, including tumoural ones. A single drug dose contains at least 50 million activated CD54 + cells and 3 doses are administered in total, each two weeks [32].

Checkpoint inhibitors have not yet been proven to be effective in prostate cancer, many studies still being in progress [50]. American guidelines also recommend

two immunotherapeutic agents (checkpoint inhibitors) in two particular situations: atezolizumab (Tecentrique<sup>®</sup>, Hoffmann-La Roche, Switzerland) together with carboplatin and etoposide in small cell histological variant of prostate cancer and pembrolizumab (Keytruda<sup>®</sup>, MSD Pharma, USA), used in solid tumours with DNA repair defects due to microsatellite instability [43].

#### *PARP inhibitors*

The role of BRCA1 and BRCA2 mutations in breast and ovarian cancer has been extensively studied, with synthetic lethality therapy such as targeting poly (ADP-ribose) polymerase enzyme (PARP) currently being a trending and effective therapy. The concept of synthetic lethality refers to the exploitation of vulnerabilities in tumour cells due to multiple genetic defects. Thus, approximately 20% of metastatic prostate cancers have DNA repair defects, and the BRCA2 mutation is the most common genetic alteration; these patients frequently have a Gleason score  $\geq 8$ , with lymph node involvement or metastases present at the time of diagnosis [38].

Drugs used in prostate cancer for targeting the PARP enzyme (specifically its inhibition) are olaparib (Lynparza<sup>®</sup>, AstraZeneca, UK) and rucaparib (Rubraca<sup>®</sup>, Clovis Oncology, USA) [43]. Their action interferes with AR status and its signalling pathways [54].

The randomized, open-label, phase III PROfound trial, which enrolled 387 patients, showed that patients with castration-resistant prostate cancer which progressed under enzalutamide or abiraterone therapy and presented BRCA genes mutation involved in homologous recombinant repair, and received olaparib treatment had a longer PFS interval than the control group [10]. Exceptions were only patients with PPP2R2A mutations (a gene involved in the negative control of cell growth and proliferation), who had an unfavourable risk-benefit ratio – which is why olaparib therapy is not recommended in their particular case [43].

The multicentre, open-label phase II TRITON2 study highlighted the efficacy of rucaparib in castration-resistant prostate cancer, by inducing a lasting response to treatment, in the presence of BRCA1 & BRCA 2 deletions [2].

Tests for identifying somatic or germline mutations are regarded as a standard in developed countries and a desideratum in developing countries, with personalized medicine representing the future of treatment for prostate cancer.

#### *Radium-223*

The multicentre, double-blind, randomized, phase III ALSYMPCA study, with 926 enrolled patients, demonstrated the efficacy of Radium-223 dichloride in symptomatic castration-resistant metastatic cancer with bone metastases [29]. Xofigo<sup>®</sup> (Radium-223 dichloride, Algeta ASA, Norway) is a radiopharmaceutical isotope of radium with a half-life of 11.4 days, administered intravenously at 4-week intervals. It is

absorbed by the bone much the same as calcium (chemical similarity), emits alpha particles, and forms hydroxyapatite complexes in areas with intense bone turnover, thus destroying tumour cells. The use of this radiopharmaceutical is recommended only in patients who have received at least two previous lines of treatment and never in combination with abiraterone and prednisone [38].

#### *Bisphosphonates/RANKL Inhibitors*

Widely applied in endocrinology, bisphosphonates are also useful in prostate cancer with bone metastases, due to their main action of inhibiting the activity of osteoclasts and preventing the apoptosis of osteocytes and osteoblasts. Paradoxically, bisphosphonates lead to decreased bone formation [30]. This aspect can be explained by the close interplay between resorption and formation processes, thus, when bone resorption decreases, the formation also decreases, probably as an indirect effect of bone resorption inhibition [14]. However, the use of bisphosphonates is effective only in preventing skeletal events (fractures, spinal cord compression), without increasing OS [38]. Superior to the action of bisphosphonates, but also without any impact on survival, the drug denosumab (Xgeva<sup>®</sup>, Amgen, USA) is another agent used in the treatment of bone metastases from prostate cancer. It blocks the action of the RANKL (receptor activator of nuclear factor kappa- $\beta$  ligand) protein thus inhibiting the formation, function and survival of osteoclasts [17]. Considering that the most common site of prostate cancer metastasis is the skeletal bone, the use of drugs that inhibit bone resorption still represents a standard complementary therapy in metastatic prostate cancer therapy.

#### **Conclusions**

At a glance, the comparison between the therapeutic possibilities for prostate cancer available before 2010 and the treatment options currently available shows remarkable scientific progress. Developments are on an upward trend, with multiple studies focusing on targeted therapies, immunotherapy and precision medicine. Primarily, however, the patient remains the main decision-maker, the treatment being individualized according to his needs and desires. That is why the research on prostate cancer is focused on identifying the genetic and molecular background that underlies the carcinogenesis mechanism, and which can differ from one individual to another. This deepening of knowledge, leading to the definition of molecular types and subtypes in prostate cancer, can and must be translated not only into new drugs, but also into innovative therapeutic approaches that act on the malignant proliferation, in relation to its distinctive morpho-functional characteristics and extension. The review of the advancements made in prostate cancer therapy provides a cohesive image of the

relationship between the genetic and molecular changes that appear in the prostate cell assembly and the therapeutic principles available and applicable at this time. The challenges for the development of new lines of personalized therapy are open, their support being ensured by the access to advanced technological facilities and the extension of clinical trials for validation. Consequently, solid foundation for a rapid dynamics of scientific achievements has been built, with undoubted further results in setting new benchmarks and standards in the treatment of this neoplasm, for the benefit of patients.

#### **Conflict of interest**

The authors declare no conflict of interest.

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