Chapter 11

Novel Therapeutic Settings in the Treatment of Castration-Resistant Prostate Cancer

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1. Introduction

Prostate cancer is the most common non-dermatological malignant disease in men in western countries. According to the American Cancer Society in 2010, the incidence of prostate cancer was 217,730 cases with 32,050 deaths from the disease [1]. Overall, the actuarial 10 and 15 years survival are 93% and 77% respectively [1]. The rise in incidence and improved survival of prostate cancer over the past decades have often been attributed to prostate cancer screening and early detection. Definite evidence supporting this relationship is, however, still pending. There are also alternative explanations such as improved treatment at advanced stages that could lower prostate cancer mortality. Because of earlier detection, up to 90% of new cases in the post prostate-specific antigen (PSA) era present with clinically localized disease, the majority of which do well regardless of treatment regimen undertaken. Overall, those with advanced prostate cancer at time of diagnosis remains essentially incurable, and do poorly after androgen withdrawal therapy developing progressive disease that is resistant to further hormone manipulation. For these patients with castration-resistent prostate cancer (CRPC), and particularly patients with metastatic disease, options till few years ago have been limited. However, as newer agents become available, higher rate of biochemical and clinical response are being achieved, providing a new hope for the management of these patients [2].

CRPC is defined as patients with serum castration levels of testosterone (< 50 ng/dL or < 1.7 nmol/L), PSA and/or clinical progression to castration, and progression despite anti-andro-

gen withdrawal for at least 4-6 weeks. PSA progression is defined as three consecutive rises of PSA, 1 week apart, resulting in two 25% increases over the nadir, with a PSA level > 2 ng/dL above the nadir. Clinical progression includes progression of bone lesions (two or more lesions on bone scan) or soft tissue progression using Respond Evaluation Criteria In Solid Tumors (RECIST) criteria [3].

Although patients with CRPC have, by definition, castrate levels of circulating testosterone, most tumors continue to remain dependent on androgen and on signaling from the androgen receptor (AR). This may occur through constitutive activation of the AR (gene amplification, alternative splicing, AR-activating gene mutations), intratumoral production of androgen, promiscuity of the AR (and binding of other hormones), activation of downstream targets by dysregulation of transcription factors (eg, binding of the frequently rearranged and overexpressed ETS oncogenic factors to androgen-regulated promoters), and alternative yet unidentified mechanisms [1, 2].

CRPC status includes patient cohorts with significantly different median survival times and different sensitivity to second hormonal manipulations. However, the vast majority of patients eventually develop progressive disease that is resistant to further hormone manipulation. We now know that although this group of patients progress to androgen deprivation, they might still be hormone-sensitive. Until 2004, cytotoxic chemotherapy was considered to be relatively ineffective in men with CRPC. In 2004, 2 landmark trials, TAX 327 and Southwest Oncology Group (SWOG) 99-16, showed for the first time a survival benefit in men with metastatic HRPC. Specifically, docetaxel-based chemotherapy demonstrated a median improvement in survival of 2.5 months as compared with mitoxantrone and prednisone in metastatic HRPC [4, 5]. Regimens that include docetaxel, have demonstrated higher rates of objective and biochemical PSA response, as well as longer survival durations. In contrast, metastatic CRPC has become a more complicated disease to be properly treated. Since then, newer treatments in this stage of the disease have been approved optimizing survival and quality of life.

2. Mechanisms involved in the development and progression of the disease

To understand prostatic growth in diseased states, it is important to understand the hormonal influences at play in normal prostate development and function. Testosterone is the primary circulating androgen in men. Within the prostate, testosterone is converted to a more potent androgen dihydrotestosterone (DHT) by the action of intracellular 5α-reductase enzymes [6]. Circulating DHT levels are low (1 : 10) when compared with testosterone, whereas in the prostate, this ratio is reversed, making DHT the primary prostatic androgen [7].

Dihydrotestosterone is essential for the development of the prostate gland. Inside the prostate, both testosterone and DHT bind to the androgen receptor (AR), stimulating the AR signalling axis that promotes cell-cycle regulation, cell survival and lipogenesis [8]. Although both the androgens are capable of binding AR, DHT has a stronger affinity than testosterone

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and a slower dissociation rate [9, 10]. DHT is also more potent at stimulating prostatic growth than testosterone [9]. These combined effects of DHT enhance the androgen signalling pathway in tissues where 5α-reductase enzymes are highly expressed [10].

Depending on the developmental stage of the individual, DHT signalling could promote the differentiation of the male external genitalia (gestation) or the maturation of the prostate gland (puberty) [7]. Throughout adulthood, DHT androgen signalling acts as a regulator of homoeostasis, maintaining the prostate epithelium by balancing cell proliferation and cell death [8]. Unlike testosterone, DHT does not exhibit an age-related decline in serum concentration. Some studies have shown a steady decline of testosterone every decade in healthy men [11, 12], whereas the levels of DHT either decline slightly or remain unchanged [13, 14]. It has been suggested that DHT levels remain constant in ageing individuals because the pathway of conversion from testosterone is saturated at low levels of testosterone. Morgentaler and Traish present a critical revision of the traditional view of T and PC [15]. They use a saturation model that is consistent with regression of cancer when T is reduced to castrate levels but lacks observed growth when serum T is increased. The saturation model starts from the observation that PCa growth is sensitive to variation in serum T concentrations at or below the castrate range and is insensitive to T variation above this concentration. Considering the actual interest in using T replacement therapies in men, a new definition of the relationship between T and PCa is of considerable importance. Evidence supports the hypothesis that T administration in hypogonadal men without PCa does not increase the risk for PCa growth if T levels are normalised [16-18].

Compelling evidence that implicates DHT as the primary prostatic androgen comes from the discovery of the Dominican pseudohermaphrodites or Guevedoce. This population has a deficiency in 5α-reductase and therefore their DHT levels are markedly lower, whereas their testosterone levels remain normal [19]. The prostate of these affected men is non-palpable and the prostate volume is one-tenth that of normal age-matched controls. Administration of DHT in these individuals results in prostate enlargement, strongly implicating DHT as a necessary component of prostate growth and development [20].

Androgen receptor signaling remains active even with castrate levels of serum testosterone, contrary to the previous notion that disease progression after gonadal ablation necessarily implied androgen-independent escape mechanisms. This is supproted by studies, which report high intratumoral androgens, continued AR signaling [21], and overexpression of enzymes key to androgen síntesis, which suggests that CRPC may synthesize androgens de novo [22, 23]. Until recently, available strategies that target the AR, such as antiandrogens, ketoconazole, estrogens or glucocorticoids, result in modest benefict. New drugs such as abiraterone, or MDV 3100 have shown a much more supression activity of the AR by different pathways.

The key components of DHT production are the 5α reductase enzymes. There are two well-characterised isoforms, type 1 and type 2 [24, 25]. Type 1 is present throughout all stages of life and is primarily localised in extraprostatic tissues including the non-genital skin, liver and certain brain regions. Although type 1 expression was originally thought to be absent from the prostate gland, certain studies have found type 1 within the prostatic tissue pre-

dominantly localised to the secretory luminal epithelium [26]. The type 2 5α-reductase isoform is prevalent in the prostatic tissue as well as the genital skin, seminal vesicle and epididymis. Although this isoform is present through all stages of prostate development, it has a single wave of expression in the skin and scalp that begins at birth and ends at ages 2–3 years [26]. Type 2 5α-reductase is deficient in the Guevedoce and therefore these individuals do not generate enough DHT to promote normal development of the prostate gland and the man's external genitalia [20].

3. Natural history of prostate cancer

Although the natural history of prostate cancer (PCa) has not been fully elucidated, it is thought to arise from damaged prostate epithelium and progressively develop over many decades [27]. Prostate disease is heterogeneous and multifocal, further complicating the understanding of its progression. Based on autopsy studies, about one-third of men over the age of 50 years display histological evidence of PCa. However, a majority of these cases remain clinically insignificant, underscoring the variability in PCa and the protracted nature of this disease [3, 28].

The likelihood of disease progression of PCa is difficult to predict. Detection of cancer from a biopsy can result in a localised diagnosis; however, upon a prostatectomy, it may be revealed that the disease had grown outside the margins of the gland or even had metastasised. Conversely, certain men diagnosed with PCa may live out their natural lives without suffering any morbidity or mortality from the disease.Therefore, it becomes imperative to determine whether or not a particular lesion will stay localised or spread beyond the confines of the gland [3]. The usually slow progression of prostate cancer allows delaying or avoiding definitive treatment (active surveillance) in selected patients if some prerequisites are fulfilled. The younger a candidate is for active surveillance, the more strict the tumour-related criteria that should be used [29].

Research has revealed insights into the likely progression of prostate tumours. It has been shown that certain high-grade tumours proceed on a more aggressive course than low-grade, well-differentiated tumours and therefore should be managed accordingly [30]. The Gleason score is one of the most powerful prognostic factors in prostate cancer [31]. In elderly patients with clinically localised, conservatively managed prostate cancer, the probability to survive the disease for at least 10 years ranges from 77% to 98% when the Gleason score is 7 or less, whereas this rate is only 33–75% in patients with a Gleason score of 8–10 [32]. The prolonged nature of PCa progression highlights the opportunities for clinical therapeutic interventions that could reduce the risk of disease development and slow it or treat the existing disease. Through the Cancer and Leukimia Group B (CALGB) cooperative study group, Halabi and colleagues performed a polled analysis combining data from 6 trials and more than 1100 patients with CRPC accured from 1991 to 2001 [33], and created a prognostic model for risk stratification of metastatic CRPC patients. The observed median survival durations (in months) were 7.5 (95% confidence interval [CI] 6.2–10.9], 13.4 (95% CI 9.7–26.3],

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18.9 (95% CI 16.2–26.3], and 27.2 (95% CI 21.9–42.8] for the first, second, third, and fourth risk groups, respectively. The factors involved in this model can be broadly divided into clinical variables that reflect the condition of the host (eg, performance status, anemia, fatigue), the tumor burden (eg, sites of metastatic disease, PSA level, alkaline phosphatase level), or the biologic aggressiveness of the cancer itself (eg, lactate dehydrogenase [LDH] levels, Gleason sum).

The clinical course of metastatic castration-resistant prostate cancer has changed considerably, primarily because of factors such as earlier diagnosis, stage migration and changes in clinical practice patterns. Earlier initiation of androgen-deprivation therapy and the increased use of diagnostic imaging have contributed to earlier detection of metastatic disease in androgen-deprived patients. Furthermore, new treatments have further extended the time to the terminal phase of the disease, extimating the duration of the course of metastatic castration-resistant prostate cancer measured from the first documented metastasis (in the castrate state) until death may now extend beyond 5 years.

4. Mechanisms and targets in CRPC

The key for the development of new drugs and to optimize androgenic suppression in advanced stages of CRPC is the identification and characterization of molecular targets and mechanisms that lead to tumor growth. Disease progression involves the development of cellular adaptive pathways of survival in an androgen-depleted environment [34]. Experimental evidence assigns an important role to the continuous activation of the androgenic receptors (ARs) in tumor growth, as well as alternative independent routes [35]. In general, resistance mechanisms can be divided into 6 groups.

- *Increased Expression of Enzymes Involved in Steroidogenesis.* Studies have suggested that, in CRPC patients, even castrate serum levels of androgen are still sufficient for AR activation and able to maintain cancer cells survival. Indeed, the intratumoral levels of testosterone in CRPC patients are equal of those found in noncastrate patients [36]. The source of these androgens is thought to be derived from the synthesis of androgens directly in prostate cancer cells due to an upregulation of the enzymes and activation of the routes necessary for the synthesis of androgens such as testosterone and dihydrotestosterone [34, 37, 38]. Also bone metastases contain intact enzyme pathways for conversion of adrenal androgens to testosterone and dihydrotestosterone [36]. Montgomery and colleagues showed that there was marked reversal of the DHT : testosterone ratio in the metastatic tumor. These tumor cells express significantly lower levels of SRD5A2, which catalyses the conversion of testosterone to DHT, and higher levels of UGT2B15 and UGT2B17, which mediate the irreversible glucuronidation of DHT metabolites. Marked up regulation of CYP19A1, which mediates the aromatization of testosterone to estradiol, was also observed in the metastases samples [34, 36-38].
- *Increased Expression of AR.* The overexpression of AR have been involved in the progression of prostate cancer [34]. The activated AR pathways observed in these CRPC patients

has been postulated as a result of genetic phenomena that promotes increased sensitivity of AR. DNA amplifications are responsible for AR overexpression and for its activation in presence of low levels of ligand (androgens) [34, 38].

- *AR Gene Mutations and Altered Ligand Specificity.* While the androgens are the main factors of tumor growth and AR signaling, the presence of AR mutations leads to its activation by nonandrogenic steroid molecules and antiandrogens [34]. The majority AR mutations are point mutations in the AR ligand-binding domain, and initially this was considered relevant to explain why 10–30% of patients receiving antiandrogens treatment experience paradoxical PSA drop on cessation of treatment [35]. However the AR mutations could occur in other regions such as the amino terminus or the DNA binding domain that confer oncogenic properties to the AR [37]. At the present, the role of AR mutations in the anti-androgen withdrawal phenomena is called into questioned and a new explanation is offered since the discovery of alternative splicing of the AR. In fact, in recent reports [39, 40], it was shown that splice variants of AR with deletion of exons 5, 6, and 7 could result in AR capable to translocate to the nucleus without ligand binding.
- *Downstream Signaling Receptor for Androgens.* One of the most important mechanisms in the development of castration resistance is the activation of different signal transduction pathways in CRPC cells. They could enhance the activity of the AR or its coactivators in the presence of low levels or even in the absence of androgen. These include other receptors such as epithelial growth factors, insulin growth factors, and tyrosine-kinase receptor [40].
- *Bypass Pathways.* The induction of bypass pathways independent of AR, is an important mechanism of castration resistance, that can overcame apoptosis induced by androgen-deprivation therapy. One such example of this is the up-regulation of antiapoptotic proteins, including the protein Bcl-2 gene [34, 40].
- *Stem Cells.* Prostatic cancer stem cells are rare and undifferentiated cells that do not express AR on their surface, being independent of androgens to survive [34]. Currently it is thought that these cells can be responsible for maintaining tumor growth and development, because they are able to survive under androgen-deprivation therapy. The identification of these cells is possible based on the expression of surface protein ($\alpha 1\beta 1$ integrin and CD133), which could allow new targets therapies [34].

5. New therapeutics settings in the treatment of castration resistant prostate cancer

Being able to predict which patients will develop metastasis and death with rising PSA levels after treatment with androgen ablation is essential for deciding therpeutic interventions and gauging prognosis. The major biologic processes under therpeutic investigation in prostate cancer involve growth and survival, chemotherapy and hormone therapy resistance, extragonadal androgen production, modulation of the androgen receptor, angiogenesis, the

bone interface, immune surveillance and escape, epigenetic regulation and stem cell renewal. A better understanding of this mechanisms responsible for prostate cancer growth and metastatic spread has allowed for the development of a wide array of new therapies.

The growth of prostate cancer is originally androgen dependent and metastatic tumors are generally treated with androgen ablation therapy, with or without antiandrogen supplementation [41, 42, 43]. However, resistance to hormonal therapy occurs within 12–18 months (remissions last on average 2-3 years, progression occurs even under castration [37, 44, 45], referred to as hormone-refractory or CRPC [41]. Resistance to hormones (in patients with metastatic disease) is probably shorter than 2-3 years, using PSA. Until recently, patients with castration-resistant prostate cancer had limited treatment options after docetaxel chemotherapy. However, in 2010, new options emerged [46]. The three nonhormonal systemic approaches that have been found to prolong survival are docetaxel as first line [4] chemotherapy, cabazitaxel as second-line cytotoxic chemotherapy [46, 47] and a vaccine named sipuleucel-T [48]. A new hormonal manipulation with abiraterone acetate [45] also showed to prolong survival in CRPC.

The current palliative treatment options for patients with CRPC can be divided in different groups such as secondary hormonal therapies, chemotherapy agents, vaccine-based immune therapy, bisphosphonates, radiotherapy and novel targets.

5.1. Antiandrogen therapies

Drugs that reduce circulating levels of androgens or that competitively inhibit the action of androgens remain central to the treatment of prostate cancer. The surgical or medical castration with orchiectomy or gonadotropin-releasing hormone (GnRH) agonists, respectively, suppresses testicular testosterone generation. However, the duration of response to castration is short [12–33 months) and, in almost all patients, is followed by the emergence of a castration-resistant phenotype [34]. The combination with antiandrogens to achieve the maximum androgen blockade (MAB) did not prove to prolong survival and 30% of the patients have a drop in PSA after discontinuing antiandrogens [3, 43]. For patients whose disease progresses after a MAB, antiandrogen can be discontinued [49], or can be switched to an alternative antiandrogen as showed in several reports [3, 43]. High-dose [150 mg daily) bicalutamide as second-line hormonal therapy resulted in ≥50% PSA reduction in 20%–45% of patients [12, 34].

- **Oral Glucocorticoids** (10 mg/day) can result in temporary PSA responses for 25% of the patients, presumably due to adrenal androgen suppression [34, 50].
- **Diethylstilboestrol** (DES), a synthetic estrogen, as well as the other estrogens, suppresses the hypothalamic-pituitary-gonadal axis and it reduces ≥50% the total PSA in 26% to 66% of patients with CRPC. However, the important thromboembolic toxicity limited is use [50,51].
- **Ketoconazol** is an antifungal agent that can be given to CRPC patients after antiandrogen withdrawal because it inhibits cytochrome P-450 enzyme-mediated steroidogenesis in testes and adrenal glands and when given at high-dose (1200 mg/day) or low dose (600

mg/day) it resulted in ≥50% PSA reduction in 27% to 63% and 27 to 46%, of patients, respectively [49]. However, the narrow therapeutic window of ketoconazole + hydrocortisone versus hydrocortisone alone must be kept in mind due to secondary effects of ketoconazole.

- **Abiraterone acetate**, a prodrug of abiraterone, is a potent and highly selective inhibitor of androgen biosynthesis that blocks cytochrome P450 c17 (CYP17] a critical enzyme in androgen synthesis in the testes, adrenals and in the tumor itself [52]. This enzyme catalyzes two sequential reactions: the conversion of pregnenolone and progesterone to their 17-α-hydroxy derivates and the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively. These two androgens are precursors of testosterone. As a result, plasma testosterone levels are significantly lower than those achieved with conventional hormone therapies; in addition, a reduction in intratumoral levels of androgens is obtained. The COU-AA-301, a phase III trial in post-docetaxel refractory CRPC, resulted in a significant improvement in overall survival in the abiraterone group [53]. Furthermore there is a second randomized phase III trial (COU-AA-302) targeting men with docetaxel and ketoconazole-naïve CRPC showing positive results in the interim analysis in the Abiraterone group, achieving a delay in disease progression and fairly long expected survival. For this reason the study was recently unblinded before completion at the recommendation of the Independent Data Monitoring Committee.

- **MDV3100** (Enzalutamide) is an androgen-receptor antagonist that blocks androgens from binding to the androgen receptor and prevents nuclear translocation and co-activator recruitment of the ligand-receptor complex. It also induces tumour cell apoptosis, and has no agonist activity. MDV 3100 was found clinically active for metastatic castration-resistant prostate cancer patients in ongoing phase I and II trials. The AFFIRM trial (a phase III trial) compared MDV3100 versus placebo in patients with docetaxel-refractory CRPC [34, 54]. The trial will determine the effectiveness of enzalutamide in patients who have previously failed chemotherapy treatment with docetaxel. In November 2011, this trial was halted after an interim analysis revealed that patients given the drug lived for approximately 5 months longer than those taking placebo, estimating a median survival of 18.4 months for men treated with MDV3100, compared with 13.6 months for men treated with placebo. This translates into a 37% reduction in the risk for death with MDV3100 (hazard ratio, 0.631]. As a result, the trial's Independent Data Monitoring Committee recommended that AFFIRM should be stopped earlier and that men who were receiving placebo should be offered MDV3100. The recommendation was based on the fact that the study's prespecified interim efficacy stopping criteria were successfully met. The committee also examined the safety profile to date and determined that MDV3100 demonstrated a risk/benefit ratio that was favorable enough to stop the study. It is expected to file for FDA approval sometime in 2012. There is another phase III trial, known as PREVAIL, that is investigating the effectiveness of enzalutamide with patients who have not yet received chemotherapy [55].

- **Orteronel** (TAK-700]. Is an androgen synthesis inhibitor. It selectively inhibits the enzyme CYP17A1 which is expressed in testicular, adrenal, and prostatic tumor tissues. It is

a very promising drug, but we still have to wait for results of two phase III clinical trials currently recruiting participants in CRPC patients and high risk patients [56].

5.2. Chemotherapy

Cabazitaxel is a new tubulin-binding taxane that has shown to be as potent as docetaxel in cell lines, and is the first chemotherapy shown to improve survival in patients with docetaxel-refractory metastatic castration resistant prostatic cancer. Moreover, it has demonstrated antitumor activity in models resistant to docetaxel due to its poor affinity for the ATP-dependent drug efflux pump, a member of the multidrug resistance protein family [57]. The TROPIC trial, a phase III trial in post-docetaxel refractory CRPC, compared cabazitaxel plus prednisone versus mitoxantrone plus prednisolone, in patients with docetaxel-refractory prostate cancer concluding in a significant improvement in overall survival in the cabazitaxel group.

Epothilones, namely, ixabepilone and patupilone, have shown significant activity in men with CRPC [58, 59]. These molecules were evaluated in second-line chemotherapy in two phase II trials after progression with prior taxane [60, 61]. Phase III trials with ixabepilone are in development and two phase II trial of patupilone are completed [59].

Eribulin mesylate (E7389] is a synthetic analog of the marine macrolide halichondrin B, which acts as a novel microtubule modulator with a distinct mechanism of action (different from taxanes) [60]. An open-label, multicenter, single-arm, phase II study was conducted in patients with CRPC stratified by prior taxane therapy [62]. Primary efficacy endpoint was PSA response rate defined as two consecutive ≥50% decreases in PSA levels from baseline. The secondary endpoints were duration of PSA response rate and objective response rate by RECIST criteria. One hundred and eight patients were available for analyses. Of these 50 were taxane pretreated. Eribulin showed activity in patients with metastatic CRPR, especially in those with taxane naïve disease. Side effects, mainly hematological toxicity (grade 3 and 4 leucopenia and neutropenia), fatigue, and peripheral neuropathy were manageable [62].

Satraplatin (JM-216] is an oral third-generation platinum compound evaluated in the SPARC trial, a phase III trial, in combination with prednisone in second-line therapy after docetaxel [34, 51]. In this trial, satraplatin plus prednisone resulted in significant improvement in PFS (11.1 weeks versus 9.7 weeks) but there were no improvement in median overall survival compared with prednisone alone (61.3 weeks versus 61.4 weeks).

Other chemotherapy treatments, studied in CRPC are Mitoxantrone with two pivotal studies in the late 90´s that could not demonstrate to be superior to palliative corticosteroid therapy. Encourarging results with alternative treatments, including Vinorelbine, a semi-synthetic vinca alkaloid, and oral cyclophosphamide, have being obtained in prospective clinical phase II trials. However the lack of representative randomized phase III trials and unknown long-term efficacy are the major problems associatied with all these studies [63, 64, 65].

5.3. Vaccines-based immunotherapy

Sipuleucel-T is an active cellular immunotherapy consisting of autologous peripheral-blood mononuclear cells, including antigen-presenting cells (APCs), which have been activated ex

vivo with a recombinant fusion protein known as PA2024, composed of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF). In the first two randomized trials, sipuleucel-T, the primary endpoint was not accomplished since these studies did not show a significant effect on the time to disease progression comparing with placebo. Despite this, the hazard ratios were in favor of sipuleucel-T [66, 67]. The IMPACT trial, a phase III trial in CPRC asyntomatic patients, resulted in a longer median survival time in the Sipuleucel-T group, with limited toxicity. Approved by the Food and Drugs Administration (FDA), currently Sipuleucel-T is not approved to been used in Europe [68].

GVAX (CGI940/CG8711] is a cellular vaccine composed of two allogeneic prostate cancer cell lines (LNCaP and PC-3] that is genetically modified to secrete GM-CSF [69]. This vaccine showed clinical benefit with limited toxicity in phase I and II trials [70, 71]. However, the two phase III trials (VITAL-1 and VITAL-2] evaluated GVAX against docetaxel plus prednisone in naïve CRPC and both were closed prematurely [70]. The VITAL-1 study was closed when the unplanned futility analysis revealed a <30% chance of meeting its predefined primary endpoint of OS improvement and the VITAL-2 terminated when an interim analysis revealed more deaths in the GVAX arm than in the control [71].

PROSTVAC-VF is a cancer vaccine consisting of a recombinant vaccinia vector as a priming immunization with subsequent multiple booster vaccinations, using a recombinant fowlpox vector. This agent presented in the context of 3 costimulatory molecules (ICAM-1, BLA-7, and LFA-3] which, when taken together, demonstrate an increase in strength of the target immunologic response [48]. This vaccine was evaluated in phase I and II trials. The phase I trial showed PSA stabilization in 40% of patients and limited toxicity and, in the phase II study, patients in the PROSTVAC-VF arm achieved an 8.5-month improvement in median OS [25.1 months versus 16.6 months) and a 44% reduction in the death rate (Hazard ratio 0.56], [72]. Phase III trial are being planned and other vaccines are under current development [73].

5.4. Bone-targeted treatments

Zoledronic Acid. Metastatic prostate cancer has an affinity to spread to the bone. Bone metastases occur in up to 90% of patients with HRPC. These metastases can lead to significant morbidity, including severe pain, fractures, and spinal cord compression tumors in the bone may cause pain, compression, or pathologic fratures, known as skeletal related events (SRE´s). Because of the frequent involvement of vertebrae by metastatic prostate cancer, the incidene of cord compression is of particular concern. Zoledronic acid has been shown to prevent or delay skeletal complications in men with bone metastases, as well as to palliate bone pain [74, 75]. At an average followup of 24 months, there was a significant reduction in the frequency of skeletal related events (SREs) in men receiving zoledronic acid compared to placebo [38 versus 49 percent), and the median time to develop an SRE was significantly longer with zoledronic acid [488 versus 321 days) [76]. Biphosphonates may also have a role in preventing osteopenia that frequently accompanies the use of androgen-deprivation therapy [77, 78]

Denosumab. Is a human monoclonal antibody directed against RANKL that inhibits osteoclast-mediated bone destruction. In a phase III study [79]. Denosumab showed to be better

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than zoledronic acid for the prevention of skeletal-related events. Although is not yet available in Europe, it is expected to be approved soon.

5.5. External beam radiotherapy and radioisotope drugs

Focal external beam radiation therapy (RT) is a palliative treatment possibility that should be considered for men with CRPC and bone pain that is limited to one or a few sites. Several clinical trials as well as a systematic review of the literature suggest that single treatments with fractionation schedules provide palliation with cost effectiveness and patient convenience [80].

Hemibody RT could also be considered in selected patients with symptomatic disease limited to one side of the diaphragm, in order to rapid pain relief, when multiple bone metastases are present [81]. However, this technique has frequently been replaced by the administration of radioisotope pharmaceuticals which may be associated with less toxicity and are more appropriated for patients with multiple painful lesions [82]. In order for these patients to be treated with radioisotopes the presence of uptake on bone scan due to metastatic disease at sites that correlate with pain is necessary. These radioisotopes are used in men with advanced prostate cancer with osteoblastic bone metastasis. These patients are often characterized by a high ratio of bone to soft tissue metastases. Multiple radioisotopes have been used but the most extensive data are with 89-strontium (89Sr), Radium-223 and 153-samarium [153Sm). Several clinical trials provide the rational for the use of this approach in carefully selected patients [83, 84, 85].

Lexidronam (Samarium 153]. Is a complex of a radioisotope of the lanthanide element samarium with the chelator EDTMP. Particularly useful in patients with CRPC and multiple painful bone metastases, who have relapsed following initial course of hormonal or cytotoxic chemotherapy, and in patients with progressive or recurrent symptoms at the treated sites. The goal in this stage of the disease is to maintain quality of life while managing the symptoms of the progressing cancer. Extensive data support the use of Samarium SM 153 in this group of patients [8, 9].

Alpharadin (Radium-223]. Alpharadin uses alpha radiation from radium-223 decay to kill cancer cells. Radium-223 naturally self-targets to bone metastases by virtue of its properties as a calcium-mimic. Alpha radiation has a very short range of 2-10 cells (when compared to current radiation therapy which is based on beta or gamma radiation), and therefore causes less damage to surrounding healthy tissues (particularly bone marrow). Radium-223 has a half life of 11.4 days, making it ideal for targeted cancer treatment. Furthermore, any Alpharadin that is not taken up by the bone metastases is rapidly cleared to the gut and excreted. In the phase III ALSYMPCA trial [86], Alpharadin succesfully met the primary endpoint of overall survival. When compared with placebo, Radium-223 was associated with improved overall survival (median 14.0 versus 11.2 months; HR, 0.69. A recent phase III trial envolving Alpharadin, showed a significant improvement in the median overall survival in chemo-naïve patients as well as in those treated previously with docetaxel.

5.6. Antiangiogenic strategies

Bevacizumab. Tumor angiogenesis is likely to be an important biologic component of prostate cancer growth and progression. An elevated levels of the potent angiogenic molecule vascular endothelial growth factor (VEGF) have been shown to correlate with advanced clinical stage and survival. Microvessel density in clinically localized prostate cancer is an independent prognostic for progression and survival [87, 88]. Antiangiogenic agents using monoclonal antibodies to VEGF, such as bevacizumab (Avastin®) have been studied in prostate cancer. Although single-agent studies have failed to demonstrate significant results, a phase II trial conducted by the CALGB added bevacizumab to docetaxel and estramustine in men with HRPC; 79% of patients had a greater than 50% decline in PSA level, median time to progression of 9.7 months, and overall median survival of 21 months [89]. On the basis of these promising results, a randomized, double-blind, placebo-controlled, phase III trial has been designed comparing docetaxel 75 mg/m^2 every 3 weeks with prednisone 10 mg orally daily with either bevacizumab 15 mg/kg IV or placebo every 3 weeks (CALGB 90401]. The primary endpoint for this trial is overall survival, and secondary endpoints include progression-free survival, PSA reduction, and grade 3 toxicities. This trial opened in April 2005 and is actively accruing.

Thalidomide. Is a synthetic glutamic acid derivative. Thalidomide was noted to have anti-inflammatory, immunomodulatory and antiangiogenic effects. alone or in combination with docetaxel were studied in phase II trials with promising results. Microvessel density (MVD) has been reported to be higher in prostate cancer tissue than in adjacent hyperplastic or benign tissue [90]. Preclinical evidence also suggests that angiogenesis may play a key role in the development of aggressive prostate cancer lesion [91]. Clinical studies have observed a correlation between increased angiogenesis in primary tumor specimens and the future development of metastatic disease. The apparent importance of angiogenesis in the evolution of prostate cancer provides a rationale for the investigation of antiangiogenesis agents in CRPC. A phase II trial of thalidomide resulted in a > 40% fall in PSA levels in 27% of patients and improvement in clinical symptoms in all responding patients. PSA declines often resulted in striking reductions in measurable disease on positron emission tomographic scan. Thalidomide plus docetaxel versus docetaxel monotherapy, in a phase II trial in patients with metastatic CRPC, showed a ≥50% PSA decrease (53% versus 37%) and improvement in median overall survival (28.9 months versus 14.7 months) for patients in the thalidomide group [92, 93].

The combination of docetaxel, thalidomide, bevacizumab, and prednisolone was also evaluated in a phase II trial with a ≥50% PSA reduction in 89.6% of patients. The median time to progression was 18.3 months and the median overall survival was 28.2 months [93]. More studies are needed before prescribing angiogenesis inhibitors outside clinical trials.

5.7. Other targets

Dasatinib. Is a small molecular kinase inhibitor of Src family kinases (SFK), being studied for prostate cancer because Src signaling is involved in androgen-induced proliferation. In a phase II trial in chemotherapy-naïve patients with metastatic CRPC, dasatinib [100 mg orally

twice daily) showed lack of progression in 43% of patients at week 12 and in 19% in patients at week 24. It also revealed a decrease in the markers of bone metabolism (N-telopeptide and bone alkaline phosphatase) A randomized phase III trial with dasatinib plus docetaxel is ongoing [94].

Ipilimumab. Blockade of the T-cell inhibitory receptor CTL-associated antigen-4 (CTLA-4] augments and prolongs T-cell responses and is a strategy to elicit antitumor immunity [95]. Ipilimumab, an anti-CTLA-4 antibody, was tested in order to potentiate endogenous antitumor immunity to prostate cancer through combination immunotherapy with CTLA-4 blockade and GM-CSF [96]. The results showed that this combination immunotherapy can induce the expansion not only of activated effector CD8 T cells *in vivo* but also of T cells that are specific for known tumor-associated antigens from endogenous immune repertoire.

In a pilot trial of CTLA-4 blockade with ipilimumab patients with CRPC were given a single dose of 3 mg/kg [95]. Results showed that this approach was safe and did not result in significant clinical autoimmunity. PSA modulating effects presented need further investigation in order to be fully understood. Two phase III trials are now recruiting patients in order to compare ipilimumab with placebo [96]. One trial [97] will evaluate this approach in patients with metastatic disease, with at least one bone metastasis, prior treatment with docetaxel, and castrate levels of serum testosterone. The other trial [98] will include patients with metastatic castration-resistant prostate cancer who are asymptomatic or minimally symptomatic and who have not received prior chemotherapy or immunotherapy.

Atrasentan. The Endothelins (ETs) constitute a family of three 21-amino-acid peptides (ET-1, ET-2, and ET-3] that are synthesized as propeptides and are transformed to their active forms by sequential endopeptidase and ET-converting enzyme-mediated cleavage [99]. ETs are regulators of cell proliferation, vasomotor tone, and angiogenesis. The ETs bind to two receptors, endothelin-A (ET-A) and endothelin-B (ET-B), and play an important role in angiogenesis, proliferation, escape from apoptosis, invasion, tumor growth, new bone formation, and bone metastasis [73, 74]. ET and their receptors have emerged as a potential targets in CRPC [99]. Efficacy and safety of ET-A receptor blockade—atrasentan (ABT-627]—have been evaluated in a double-blind, randomized, placebo-controlled, phase II trial [99], Two hundred and eighty-eight asymptomatic patients were randomized to one of three study groups: placebo, 2.5 mg atrasentan, 10 mg atrasentan. Primary endpoint was time to progression. Secondary end points were time to PSA progression, bone scan changes, and changes in bone and tumor markers. Target therapy with atrasentan was well tolerated and results showed a potential to delay progression of CRPC.

Based on these results other phase III studies also evaluated atrasentan. In one of these studies [100], atrasentan did not reduce the risk of disease progression relative to placebo. However exploratory analyses showed that alkaline phosphatase and PSA levels were significantly lower in the treatment arm [90]. Another phase III study (SWOG S0421] tested atrasentan combined with docetaxel/prednisone in metastatic CRPC as a first-line therapy [100]. SWOG trial S0421 closed earlier based on interim finding that atrasentan added to docetaxel and prednisone did not confer additional survival benefit to patients with hormone-refractory prostate cancer. The Data and Safety Monitoring Committee has determined that

patients in phase III S0421 receiving atrasentan in addition to a standard chemotherapy regimen for advanced prostate cancer did not have longer survival or longer progression-free survival.

Zibotentan (ZD 4054]. Is another ET-A receptor antagonist, which showed evidence of activity in a randomized phase II trial in men with castrate-resistant prostate cancer and bone metastases [101]. Following these results two phase III trials [102, 103] were conducted. ENTHUSE M0 was discontinued following the results of an early efficacy review by the Independent Data Monitoring Committee. The company has concluded that zibotentan was unlikely to meet its primary efficacy endpoints progression free survival and overall survival. Results from ENTHUSE M1C are still awaited.

Tyrosine kinase inhibitors (TKIs) are important new class of target therapy that interfere with specific cell signaling pathways and thus allow target specific therapy for selected malignancies. Sorafenib and sunitinib have been tested in prostate cancer in phase I and II trials.

Sorafenib. In the first stage of a phase II trial with sorafenib [104] 22 metastatic CRPC were enrolled. Most of the patients [59%) had received prior therapy with docetaxel or mitoxantrone. Sorafenib therapy failed to show >50% PSA reduction [51]. A second stage of the trial was conducted with 24 more patients [105]. Of the 24 patients, 21 had previous chemotherapy with docetaxel. All patients had bone metastases, either alone (in 11] or with soft-tissue disease (in 13]. At a median potential followup of 27.2 months, the median progression-free survival was 3.7 months and the median overall survival was 18.0 months. For the whole trial of 46 patients the median survival was 18.3 months. The authors concluded that sorafenib has moderate activity as a second-line treatment for metastatic castration-resistant prostate cancer in this trial population [106].

Another phase II study [98] included 57 chemotherapy naïve CRPC patients. Fifty-five patients were evaluable. Two of these patients had >50% PSA reduction and 15 patients had stable disease. Analysis of the results from a third phase II trial suggests that sorafenib therapy could affect PSA production or secretion regardless of its antitumor activity [107].

Sunitinib. A phase I/II trial of sunitinib in combination with docetaxel and prednisone showed a PSA response in 56% of patients, a median time to PSA progression of 42.1 weeks, and a partial response of measurable disease in 39% patients [108]. Sunitinib was also tested in CRPC naïve and docetaxel refractory patients in other phase II trials [106, 107]. A phase III trial comparing sunitinib plus prednisone versus prednisone alone, in patients with docetaxel refractory metastatic CRPC, is ongoing. Overall survival is the primary endpoint of this study [109].

Cabozantinib. Is an inhibitor of MET and VEGFR2 [90]. Both the MET and VEGF-type 2 receptor signaling pathways appear to play important roles in the function of osteoblasts and osteoclasts. MET signaling promotes tumor growth, invasion, and metastasis. Results from cabozantinib trial were presented at ASCO Meeting, 2011. The authors concluded that cabozantinib showed clinical activity regardless of prior docetaxel in metastatic CRPC patients, particularly in patients with bone disease, in addition to improvements in hemoglobin and tumor regression.

There are also other potential targets, such as IGF-1R signaling, vitamin D receptor, PTEN, and phosphoinositide 3-kinase signaling; those are quite promising and could lead us to new treatment options [3, 34]. New mechanisms, drugs, and clinically relevant molecular targets show survival advantage and are new options available for patients after traditional chemotherapy. As ongoing studies using all the mentioned agents continue to evolve, our understanding of how and where these agents fit into the treatment paradigm for patients with CRPC will become clearer. Improvements in progression-free survival and OS rates, observed with novel agents, in metastatic prostate cancer have led to a shift in treatment paradigm. The challenge will be to position the current established and expected novel treatments in the new landscape of metastatic prostate cancer and to determine at what point and time in the disease course they can best be administered. It is clear, however, that our knowledge of the biologic mechanisms involved iin teh progression of metastaic castration-resistant prostate cancer has reached a level at which the discovery of more effective targeted approaches will probably futher improve outcomes.

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