14

Prostate Cancer: Current and Emerging Therapies

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1. Introduction

Prostate cancer (PC) is the second most prevalent cause of death in men in the USA and Europe. The dependence of PC on androgens has been recognized for more than 7 decades. Medical and surgical androgen deprivation therapy (ADT) has been a standard palliative therapy for metastatic PC. However, an estimated 217,730 new cases and 32,050 PC related deaths in the USA alone in 2010 despite ADT, make the need for finding new targets and novel therapies an absolute priority [1]. Despite medical treatment, the vast majority of patients with metastatic prostate cancer inevitably progress and die from their disease. While initially majority of metastatic prostate cancers rely on the availability of androgens for growth and survival, in their final stages of disease, these patients eventually progress clinically under androgen-deprived conditions. Under the selective pressure of drug treatment, prostate cancer cells are then able to acquire molecular changes that allow them to survive androgen-deprived conditions, gain a selective growth advantage, and finally, result in progression of disease. Our knowledge about this disease is increasing. However, the cellular and molecular events that are necessary to cause progression of prostate cancer from an androgen-dependent (AD) to an androgen-independent (AI) state of disease are not completely understood.

With a 9% response rate, chemotherapy was once thought to play a clinically insignificant role in metastatic and castration resistant prostate cancer (CRPC) [2]. More recently, however, a role has emerged for systemic chemotherapy after the demonstration of a small but significant survival benefit for taxane-based chemotherapy in the two landmark studies, TAX-327 and SWOG-9916 [3, 4]. Since median survival for patients with metastatic CRPC is still only about 18 months, there is plenty room for further improvement. Moreover, there is a strong need for second and third-line regimen for patients progressing after docetaxel, and these patients should be enrolled into clinical trials.

2. Novel biomarkers

PC is a highly curable disease if diagnosed at an early stage and 5-year relative survival rates based on Surveillance, Epidemiology, End Results (SEER) database's cancer statistics

were 100.0% for both localized and regional disease, and 30.6% for distant metastatic disease [5]. Given the enormous importance of early detection, selection of biomarkers for early diagnosis and monitoring the treatment are absolutely essential. Traditionally, serum prostate specific antigen (PSA) has been used as biomarker. However, in about 10% of patients, whose tumors are associated with low serum prostate PSA, a decline in PSA cannot be used as an indicator of response. Several studies also suggest that serum PSA level does not reflect PSA levels in the tumor tissue or the growth of tumor [6]. Therefore, there is an urgent need to find out new biomarkers that may be more useful in diagnosis of PC.

2.1 Fluoro-dihydrotestosterone (FDHT)

FDHT is a biomarker of androgen receptor expression in human prostate cancer, and has been particularly useful in the setting of advanced prostate cancer, when the patient has castrate levels of circulating testosterone in the blood. Two small prospective studies have shown the feasibility of using FDHT scan with excellent imaging characteristics and a rapid uptake in the tumor at metastatic sites expressing androgen receptor with acceptable dosimetry [7, 8]. This scan is currently incorporated and compared to fluoro-deoxyglucose (FDG) positron emission tomography (PET) in a phase I/II study of CRPC that are being treated with chemotherapy [9]. This study uses PET scans, which is a type of imaging test that uses a radiotracer, to see whether these scans may be better able to find places in the body where prostate cancer cells may have spread. Initial reports presented at the 2009 ASCO annual meeting showed a > 50% decline in the standardized uptake value (SUV_{max}) on FDHT PET observed in 11 out of 12 of patients (92%) at 4 and 12 weeks, while 6 patients (50%) had a decreased SUV_{max} on FDG PET [10].

2.2 Circulating tumor cells

Circulating tumor cells (CTCs) are epithelial cells that shed from tumors. The CTC count is based on a test that works by using fluorescence labeled antibodies against epithelial cell adhesion molecules combined to microscopic iron particles, called ferrofluid [11]. These antibody/ferrofluid combinations attach very specifically to CTCs. Powerful magnets then "pull" the CTCs out of the blood sample and they are then stained with additional bio-molecules and chemicals so that they can be positively identified as CTCs [12]. This system, approved by the US Food and Drug Administration (FDA) is commercially available as CellSearch™ for monitoring of metastatic prostate cancer, metastatic breast and metastatic colorectal cancer patients [13]. In a prospective study, De Bono and colleagues [14] reported that CRPC patients with ≥ 5 CTCs per 7.5 mL of blood prior to chemotherapy had a significantly shorter median survival compared to those with < 5 CTCs (10 *vs.* 21 months). Also, changes in number of CTCs following chemotherapy correlated with prognosis. Patients who had < 5 CTCs at baseline and at their last assessment had a median survival of more than 26 months, while those who had ≥ 5 at baseline but then had < 5 at their last assessment had a median survival of 21 months. In contrast, those with < 5 CTCs at an early assessment who had ≥ 5 at their last assessment had a median survival of 9 months, and those who had ≥ 5 CTCs at all assessments had a median survival of only 7 months. Two recent prospective studies have also validated that increased levels of circulating tumor cells predict worse outcomes in patients with metastatic CRPC [14]. Thus, CTC number, analyzed as a continuous variable, has a potential to be used to monitor disease status and might be useful as an intermediate endpoint of survival in clinical trials.

2.3 Clusterin

Clusterin is a stress-induced cyto-protective chaperone protein expressed in virtually all human tissues. Clusterin over-expression is demonstrated in various human malignancies including prostate, breast and colon cancers [15, 16]. It has been shown that in prostate cancer, clusterin levels are low in hormone-naïve tissue, but increase significantly after hormone therapy [17]. Clusterin levels have also been correlated with preoperative PSA value and also the pathological grade on both biopsy and radical prostatectomy specimens. Further, clusterin expression has also been reported to be a possible predictor for biochemical recurrence following radical prostatectomy [18]. In a recent phase II clinical trial, serum levels of clusterin was used a biomarker of response and was reported to be significantly reduced following treatment with OGX-011, an antisense oligonucleotide against clusterin [19]. All these data suggest that serum clusterin level could be used as a potential diagnostic and prognostic indicator and also a marker of response to treatment in CRPC with metastases.

3. Androgen Deprivation Therapy (ADT)

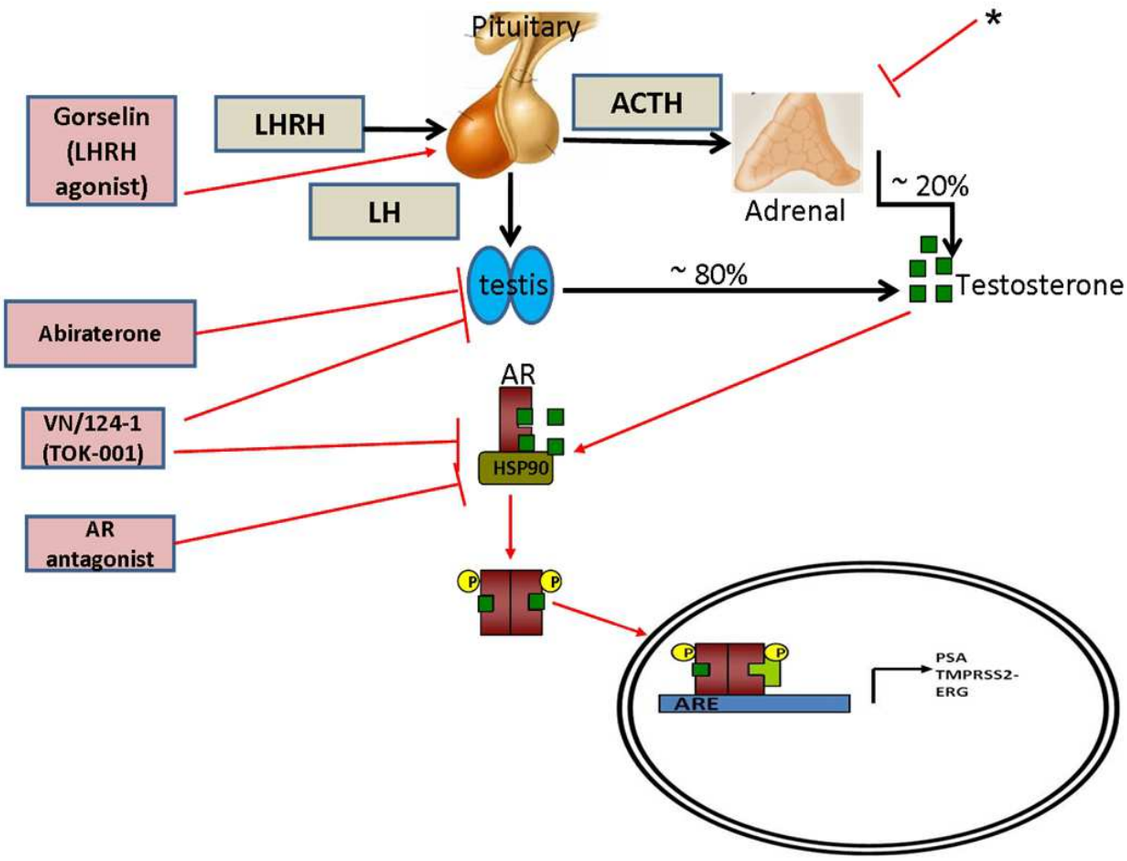
ADT is the cornerstone treatment of advanced prostate cancer. In 1941, Huggins and Hodges first noted the beneficial effects of castration [20]. In addition to its well established role in treating patients with metastatic disease, ADT is sometimes used to treat patients with increasing PSA levels after local treatment, even without radiographic or other evidence of metastatic disease. It is also used as adjunct therapy for men undergoing radiation therapy for high-risk localized disease. Several large-scale phase III studies reported in the 1980s have shown that the suppression of plasma testosterone by medical or surgical castration in men with advanced or metastatic prostate cancer leads to symptom reduction, and a marked clinical response [21].

Several studies have attempted to pharmacologically target androgenic stimulation at different points in the hypothalamus-pituitary-testis-AR pathway. The goal of these drug interventions is to slow disease progression, and to treat the disease. **Surgical castration** completely eliminates testosterone production by the testes, whereas administration of an **LHRH agonist** (medical castration) generates castrate levels of serum testosterone (< 20 or < 50 ng/dL respectively) by having a negative hormonal feedback on the hypothalamus [22]. There was no statistically significant difference in disease free or overall survival for metastatic patients treated with either of the these testosterone lowering treatments [23]. Conventional ADT was associated with a number of adverse effects like hot flashes, loss of libido, decreased quality of life.

AR antagonists and CYP 17 inhibitors are some of the newer ADT therapies. Figure 1 is a schematic representation of agents that target the AR signaling.

3.1 Androgen Receptor (AR) antagonism

There is ample evidence in the literature that prostate cancer growth can be inhibited by blocking the AR. AR antagonists compete with dihydrotestosterone (DHT) for binding to the AR and thus block AR signaling. Despite the significant reduction in circulating testosterone, castration does not affect adrenal androgen production. Therefore, anti-androgens were introduced to directly prevent the binding of testosterone and DHT to the AR. Anti-androgens competitively inhibit ligand binding to the AR and may also prevent ligand-independent AR activation through various pathways, such as inhibiting the recruitment of



*Abiraterone and VN/124-1 (TOK-001) also inhibit the synthesis of adrenal androgens. Gorselin inhibits secretion of LH from the pituitary. Abiraterone and VN/124-1 (TOK-001) inhibit CYP17 enzyme. VN/124-1 (TOK-001) also antagonizes AR.

Fig. 1. Schematic representation of AR regulation in prostate cancer and agents targeting AR signaling.

coactivators or activating corepressors [24]. Anti-androgens are typically classified as steroidal or nonsteroidal based on their respective chemical structures [25]. The major anti-androgens in clinical use worldwide are the nonsteroidal bicalutamide, flutamide and nilutamide and the steroidal cyproterone acetate (CPA) **(Figure 2)**. CPA is used in Europe, but is not commercially available in the USA. CPA is one of the least studied anti-androgen. Conversely, bicalutamide is the most extensively studied nonsteroidal anti-androgen [26]. Lowered percentages of hot flashes as compared with castration have been reported with bicalutamide, flutamide and CPA treatment. Patients treated with bicalutamide have reported better preservation of sexual interest compared with LHRH agonist alone [27]. It is also important to note that a meta-analysis of randomized trials comparing CPA and ADT with ADT alone showed a survival decrease in the CPA group [28]. Overall, the nonsteroidal anti-androgens appear to be better tolerated than castration, however it is important for clinicians to explain the tolerability profiles of all treatment options in order to find an individual match for each patient [29]. Agents targeting AR that are in clinical trials are summarized in **Table 1**. As monotherapy with an AR antagonist is not yet a standard treatment for patients with advanced or metastatic prostate cancer, it has been combined

with medical (or surgical) castration, initially in studies conducted in the late 1980s and early 1990s (complete androgen blockade). These clinical trials showed that the combination of surgical or medical castration plus the administration of an AR antagonist resulted in only a limited improvement in disease-specific and overall survival in patients with advanced and/or metastasized prostate cancer compared to those who receive castration only [30].

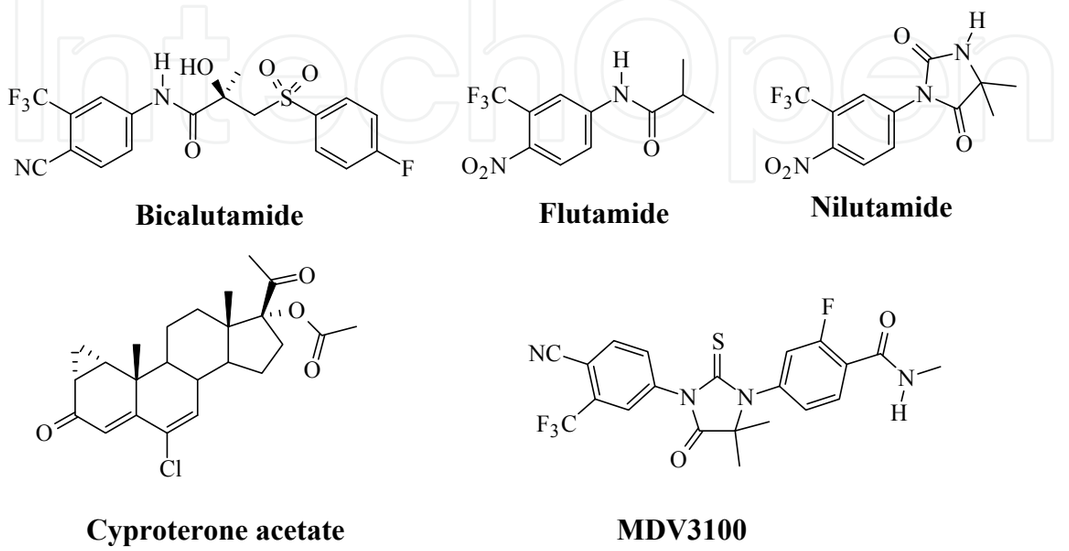


Fig. 2. Structures of currently used and anti-androgens and clinical candidate MDV3100.

3.1.1 MDV3100

Following the evidence that AR expression is increased in CRPC, the diarylthiohydantoin MDV3100 (**Figure 2**) was developed as a second-generation anti-androgen capable of sustained AR antagonism under conditions of AR over-expression. In preclinical evaluation MDV3100 was shown to bind to the AR with a five- to eight-fold higher affinity than bicalutamide [6, 31]. In a Phase I/II study in CRPC, anti-tumor activity of MDV3100 was assessed by time on treatment, PSA, soft tissue and osseous disease and circulating tumor cells (CTC). Doses of up to 600 mg/day were investigated. Out of 114 patients treated with 30–360 mg/day and followed for over 12 weeks, 65 were chemotherapy-naïve and 49 were post chemotherapy. At 12 weeks, reduced PSA levels were seen in both groups, with a 57% (37/65) decline in the naive group and 45% (22/49) in the post-chemotherapy patients [31, 32]. No progression was noted in 74% (35/47) of patients with evaluable soft tissue lesions and 62% (50/81) of patients with bone lesions. Dose-limiting toxicity was observed at 600mg/day. Fatigue was noted at 360 and 480 mg/day. Hence, the dose was reduced. At concentrations of 60, 150 and 240 mg/day, MDV3100 was well tolerated and no serious adverse events related to the drug were reported. Of the 73 patients, 63 had available CTC counts. A total of 85% of those with favorable pretreatment CTC counts maintained favorable post-treatment CTC counts and 58% of patients treated at 240 mg/day converted from unfavorable to favorable, post-treatment. Bone scans revealed stable disease in 29% (6/21) patients with osseous disease on 240 mg/day. A half-life of 1 week was established and the current reported data suggest a dose-response trend. Ultimately 240 mg/day was selected for the Phase III trials and the results are much anticipated.

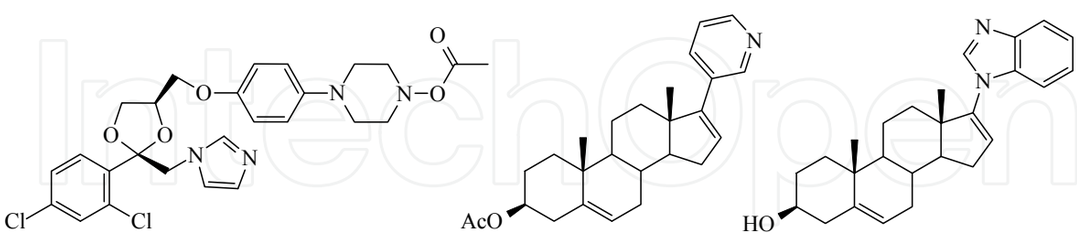
Drug	Mechanism of action	Patient characteristics	Phase of development	Clinical trial Registration number
MDV-3100	AR antagonist	Chemotherapy-treated	Phase III	NCT00974311
		Chemotherapy-naïve	Phase III	NCT01212991
ARN-509	AR antagonist	ND	Phase I-II	NCT01171898
AZD3514	AR antagonist	ND	Phase I-II	NCT01162395
Abiraterone acetate	CYP 17 inhibitor	Chemotherapy-treated	Phase III	NCT00638690
		Chemotherapy-naïve	Phase III	NCT00887198
Orteronel (TAK-700)	CYP 17 inhibitor	Chemotherapy treated	Phase III	NCT01193257
VN/124-1 (TOK-001)	AR downregulating agent, CYP 17 inhibitor and AR antagonist	ND	Phase I-II	NCT00959959

Abbreviations: ND = not defined.

Table 1. Agents targeting AR in clinical development for CRPC.

3.2 CYP17 Inhibitors

Blocking the *in situ* production of androgens by inhibition of CYP 17 enzyme is a critical key in the treatment of patients with advanced and/or metastatic prostate cancer. The structures of CYP 17 inhibitors ketokonazole, abiraterone acetate and VN/124-1 (TOK-001) are presented in **Figure 3**.



Ketoconazole **Abiraterone acetate** **VN/124-1 (TOK-001)**

Fig. 3. Inhibitors of CYP17.

3.2.1 Ketoconazole (HDK)

Ketoconazole is a broad spectrum anti-fungal agent that has been extensively used off-label as second-line hormonal therapy for prostate cancer. Ketoconazole inhibits 11-β hydroxylation, cholesterol side chain cleavage to pregnenolone and CYP17 [33]. Two single center trials on the

use of HDK in CRPC found PSA declines >50% in 55% (11/20) [34] and 63% (30/48) of patients [35]. A larger phase III study of HDK therapy in 260 patients with post-ADT metastatic PC on anti-androgen withdrawal (AAWD) demonstrated a PSA decline > 50% in 27% of patients treated with HDK plus AAWD. Overall survival was not different between the treatment groups; however, those patients with a > 50% PSA decline had a median survival of 41 months compared to 13 months for those without a PSA decline. Time to PSA progression in PSA responders was 5.9 *versus* 8.6 months in AAWD alone and AAWD+HDK groups, respectively [36]. Androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS) levels decreased with HDK therapy. However, there was no change in testosterone level from baseline in either treatment groups.

3.2.2 Abiraterone acetate

Abiraterone, a highly selective irreversible CYP17 inhibitor, was developed as a mechanism-based steroidal inhibitor of CYP17 following observations that nonsteroidal 3-pyridyl esters had improved selectivity for inhibition [37]. Abiraterone has been shown to reduce serum testosterone levels to below a detection threshold of 1 ng/dl [38]. Promising results from clinical trials of abiraterone acetate in CRPC patients have recently been reported. In a phase I trial of abiraterone acetate treatment of both ketoconazole pre-treated and ketoconazole naïve CRPC patients [4], PSA declines of ≥50% were seen in 18 (55%) of 33 patients, including nine (47%) of 19 patients with prior ketoconazole therapy and nine (64%) of 14 patients without prior ketoconazole therapy. Significantly, the anti tumor activity was nearly equivalent in both populations. The activity observed in castrate, ketoconazole naïve patients confirms that abiraterone acetate is an active agent, whereas the activity in ketoconazole pre- treated patients implies that a more selective and potent inhibitor of CYP17 may be an improvement beyond ketoconazole, or an additional sequential therapeutic option. The most common adverse events in patients treated with abiraterone acetate were fatigue, hypertension, headache, nausea, and diarrhea.

In addition to chemotherapy-naïve patients, a multi center phase II study evaluated the efficacy of abiraterone in patients with docetaxel-treated CRPC [39]. All patients were treated with 1000 mg/d. Forty seven patients were enrolled, and treatment resulted in observed PSA declines ≥ 50 % in 51 % (24/47) of patients at least once. Partial responses (by RECIST criteria) were reported in 27% (8/30) patients with measurable disease. Decreases in circulating tumor cell (CTC) counts were also observed [39].

Two phase III clinical trials of abiraterone acetate are now in progress. The first of these trials is designed to evaluate abiraterone + prednisone against a placebo + prednisone in patients with progressive CRPC after docetaxel chemotherapy. This trial has an estimated study completion date of June 2011 [40]. The second study will evaluate abiraterone + prednisone against a placebo + prednisone in CRPC patients prior to chemotherapy. The estimated study completion date is in 2014. Both trials list prior ketoconazole treatment in their exclusion criteria.

3.2.3 VN/124-1 (TOK-001)

VN/124-1 was rationally designed as an inhibitor of androgen biosynthesis via inhibition of CYP17. Utilizing intact CYP17 expressing Escherichia coli, VN/124- 1 was shown to be a potent inhibitor of the enzyme with an IC_{50} value of 300 nM compared to abiraterone which had an IC_{50} value of 800 nM. The high efficacy of VN/124-1 in several prostate cancer

models is believed to arise from its ability to downregulate the AR as well as competitively block androgen binding. In competitive binding studies against the synthetic androgen [^{3}H] R1881, VN/124-1 was equipotent to bicalutamide in LNCaP cells. Transcriptional activation assays showed VN/124-1 to be a pure AR antagonist of the wild- type AR and the T877A mutation found in LNCaP cells [6]. VN/124-1 inhibited the growth of CRPCs, which had increased AR and were no longer sensitive to bicalutamide [6].

VN/124-1 (0.13 mmol/kg twice daily) caused a 93.8 % reduction (P = 0.00065) in the mean final LAPC-4 xenograft volume compared with controls. In another anti-tumor efficacy study, treatment of VN/124-1 (0.13 mmol twice daily) was very effective in preventing the formation of LAPC4 tumors. VN/124-1 (0.13 mmol/kg twice daily) and VN/124-1 (0.13 mmol/kg twice daily) + castration induced regression of LAPC4 tumor xenografts by 26.55 and 60.67 %, respectively [6]. This impressive pre-clinical data led to further clinical development of VN/124-1 by Tokai Pharmaceutical Cambridge, Mass. Tokai Pharmaceuticals initiated ARMOR1 (Androgen Receptor Modulation Optimized for Response 1) phase 1/2 trials in castrate resistant prostate cancer patients on November 5, 2009 [41]. The results of this clinical trial are awaited. The study is expected to be completed by July 2012. The benefits of ADT in selected clinical trials are summarized in **Table 2**.

Source	Outcome	Control Arm (95% CI)	ADT-arm (95% CI)	P value
Bolla el al 1997 [42] and Bolla el al 2002 [43]	Increase in 5-yr survival	62 (52-72)	78 (72-84)	.0002
D'Amico et al 2004 [44]	Increase in 5-yr survival	78 (68-88)	88 (80-95)	.04
Messing et al 1999 [45]	Increase in 10-yr survival	49.0	72.4	.025

Table 2. Benefits of ADT in prostate cancer.

3.3 Resistance to ADT

During the development of CRPC, there is evidence that the testosterone-AR pathway is bypassed, and that prostate cancer cells find alternative ways to continue AR-mediated functions [46]. Concurrently, this renewed and continued AR activation leads to renewed cell proliferation, unsustained growth, and eventually causes the prostate cancer host to have biochemical and clinical progression of disease. Although CRPC is androgen independent, it remains dependent on a functional AR. Various mechanisms contribute to resistance to ADT. They include AR amplification, AR mutations and hypersensitivity of AR to androgens or other ligands (**Figure 4**).

3.3.1 AR amplification

One of the mechanisms by which a prostate cancer cell might escape and survive the low testosterone conditions and sustain growth is by amplification of the AR gene and by up-regulation of the AR protein [47]. CRPC expresses more AR than benign prostatic tissue and hormone-naïve prostate cancers [48]. As a consequence, even very low levels of intracellular testosterone and/or DHT might cause androgen signaling and AR-regulated transcription [49]. Several studies have reported that during the process of the tumor becoming CRPC, the AR protein has increased stability and it becomes hypersensitive to androgens [50].

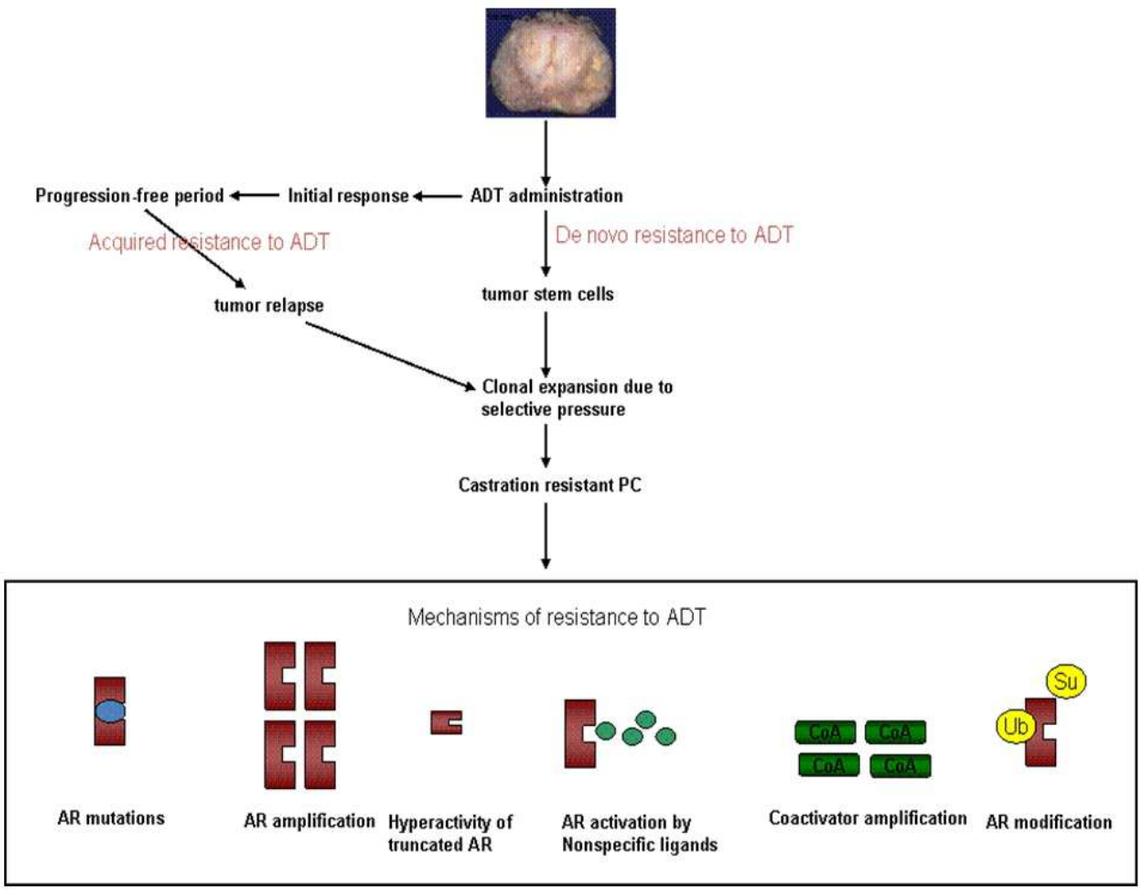


Fig. 4. Mechanisms of development of resistance to androgen deprivation therapy: Chronic ADT therapy leads to development of resistance in prostate cancer (PC) cells by various mechanisms such as activating AR mutations, AR amplification, overactive spliced / truncated AR isoforms, amplification of coactivators and modifications of AR by various physiological processes such as ubiquitylation and sumoylation.

3.3.2 AR mutations

Mutations in AR lead to change in the specificity of ligand binding. It has been reported that the mutated AR might thus be activated by other steroid hormones, such as progesterone, estrogens, adrenal androgens and metabolic by-products of DHT [51]. In other AR mutations, the AR protein might become even more promiscuous, and bind AR antagonists such as cyproterone acetate and flutamide [52, 53]. The withdrawal of flutamide in patients with CRPC, and with this the discontinuation of the activation of the AR, causes a rate of improvement of serum PSA in 30–40% of patients. This effect is now defined as the **'anti-androgen withdrawal' syndrome** [54]. The splice variant AR isoforms, expressing the NH_2–terminal domain and the DNA binding domain only, can be overexpressed in CRPC, are functionally active, promote the expression of AD genes, and might support growth of CRPC [55]. Co-activators can cause conformational changes of the AR and with this, alter the ligand binding domain (LBD) and the specificity of the AR protein [56]. Mutations in co-activator genes and/or changes in the expression of these co-activator proteins have been reported [57].

3.3.3 Hypersensitivity of AR to low levels of androgens

Recent evidence suggests that plasma levels of androgens do not correlate with intraprostatic androgen levels [58]. Also, it has been shown that despite castration levels of plasma testosterone, DHT levels in the prostate itself remain at 15–40% of that at baseline [59]. These low intraprostatic levels of DHT are still sufficient to activate the AR and stimulate the expression of androgen dependent genes [60]. Thus, even decreased levels of intraprostatic DHT might be sufficient to support biological processes that concurrently lead to cell proliferation and a defense against apoptosis. After ADT, Mizokami *et al.* [61] showed that intraprostatic androstenediol levels are similar to those in benign prostate hypertrophic tissue, and are able to activate a mutated AR. Craft et al. [62] showed *in vitro* that ADT provides for selective pressure, resulting in an outgrowth of a few AI cells. This clonal expansion of androgen independent cells then further resulted in all the cascades of CRPC. However, most androgen independent prostate cancer cells continue to express the AR, and rely on AR signaling pathways, even in ligand-independent AR activation.

4. Chemotherapy

Mitoxantrone, estramustine, and docetaxel (**Figure 5**) are the three drugs which are currently approved by the FDA for first-line chemotherapy in CRPC. In the landmark

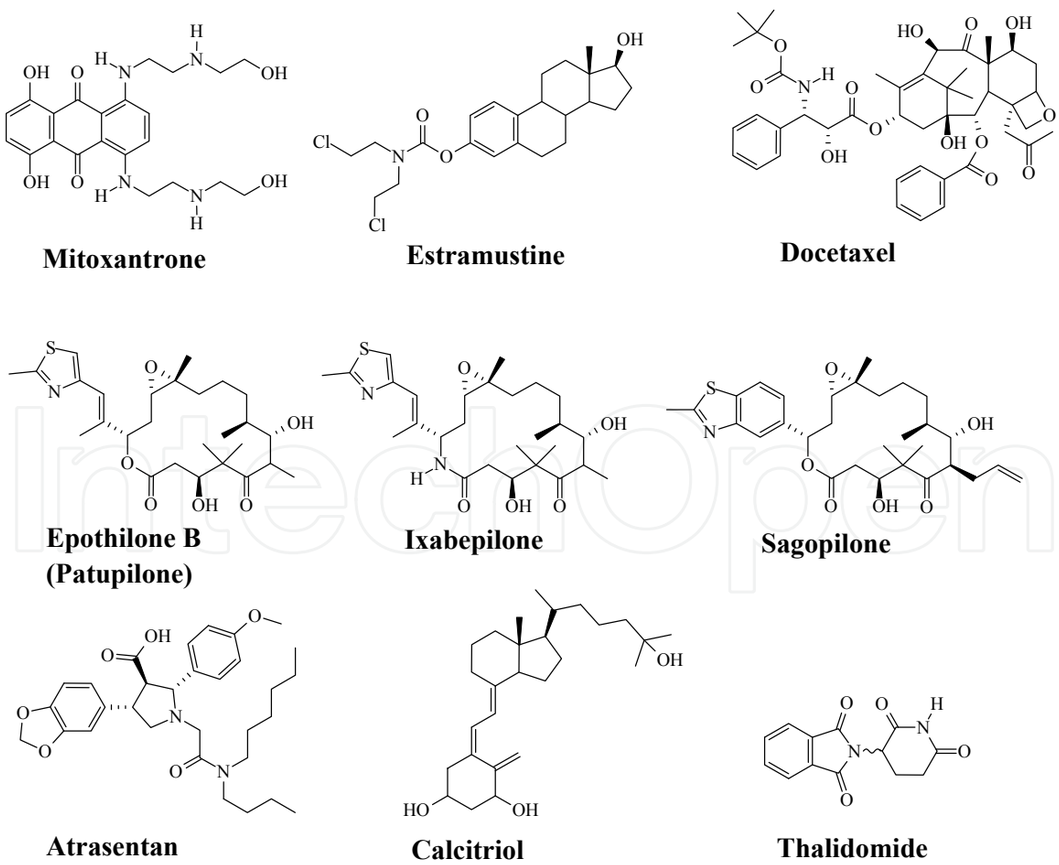


Fig. 5. Structures of chemotherapeutic agents and other types of anti-cancer agents.

TAX-327 trial, 1006 chemotherapy-naïve CRPC patients were randomized to three different treatment arms – docetaxel 30 mg/m² every week, docetaxel 75 mg/m² every three weeks and mitoxantrone 12 mg/m² every three weeks (**Figure 6**). All patients received prednisone 5 mg orally twice a day. Patients receiving docetaxel every three weeks had a significant improvement of survival compared to weekly docetaxel and mitoxantrone (18.9 months *vs.* 16.5 months; P < 0.009). PSA response, quality of life and control of pain were also significantly better with docetaxel every three weeks compared to mitoxantrone [3]. An update of the results of TAX-327 trial in 2007 showed a persistence of a survival benefit of docetaxel every three weeks compared to mitoxantrone and no survival benefit with the weekly docetaxel. At three years, survival was 17.2% for docetaxel every three weeks compared to 12.8% with mitoxantrone (P = 0.005) [3].

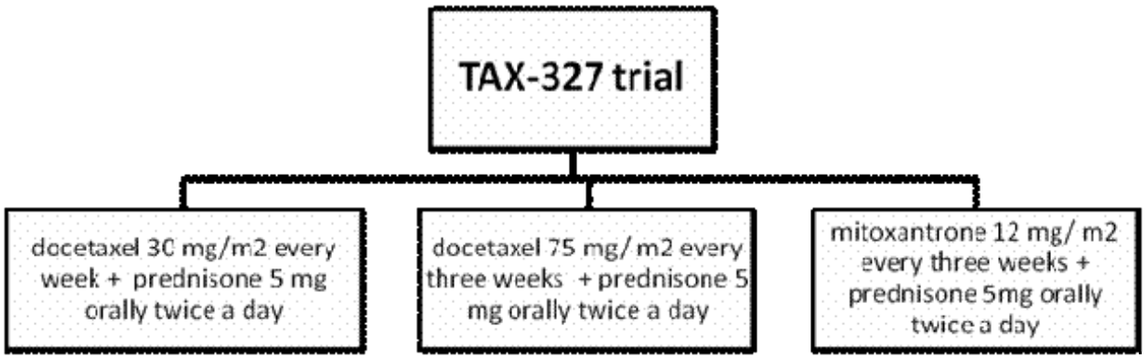


Fig. 6. Schematic flow chart of study design of TAX-327 clinical trial.

The **Southwest Oncology Group (SWOG)-9916 study** also showed survival benefit with Docetaxel. 674 patients with metastatic CRPC were randomized to docetaxel/estramustine and Mitoxantrone/prednisone arms (**Figure 7**). Treatment regimen was 280 mg of estramustine three times daily on days 1 through 5, docetaxel 60 mg/m² on day 2 in the docetaxel arm and 12 mg of mitoxantrone mg/m² on day 1 plus 5 mg of prednisone twice daily in the mitoxantrone arm. Docetaxel was reported to be superior to mitoxantrone with a median survival of 17.5 months *vs.* 15.6 months (P = 0.02), median time to progression (6.3 *vs.* 3.2 months; P < 0.001) and PSA declines of 50% (50% *vs.* 27%; P < 0.001). However, there was no significant objective tumor response difference between the two arms [4]. TAX-327 and SWOG-9916 trials showed a 20–24% reduction in mortality in patients with CRPC docetaxel-based combination chemotherapy.

Although the taxanes provide impressive results against CRPC, their survival benefits remain far from being long lasting. This is primarily due to development of resistance against the taxanes [63]. Several molecular mechanisms account for *de novo* and acquired resistance to taxane-based chemotherapy in prostate cancer. Multidrug resistant phenotype (MDR) is a common cause of *de novo* resistance. Acquired resistance to taxanes can result due to alterations in the molecular target, tubulin. Some of these mutations alter drug binding, while others cause shifts in the equilibrium of the tubulin dimer and microtubule polymer, thereby affecting taxane efficacy [64, 65]. Preclinical studies have shown that overexpression of class III β-tubulin confers *de novo* and acquired resistance to taxanes in several tumor types, as shown in prostate, breast, lung cancer cell lines [66, 67].

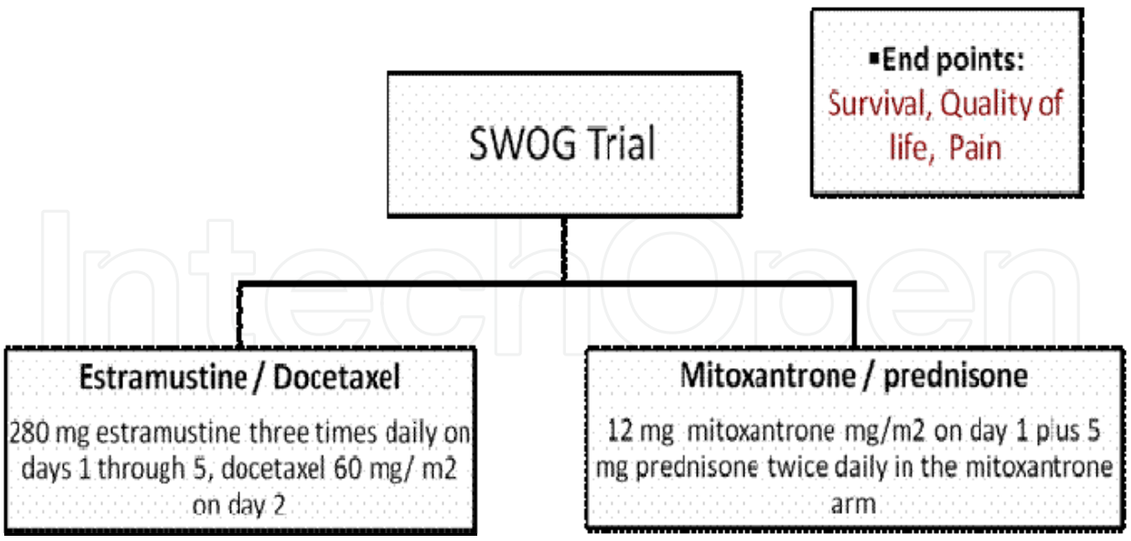


Fig. 7. Schematic flow chart of study design of SWOG-9916 clinical trial.

Drug	Mechanism of action	Primary endpoint	Clinical trial Registration number
Docetaxel/Prednisone every 3 weekly vs 2 weekly (PROSTY)	Taxane (antimitotic, antimicrotubule agent)	TTF	NCT00255606
Docetaxel/Prednisone + Dasatinib	Multi-target Tyrosine Kinase inhibitor	OS	NCT00744497
Docetaxel/Prednisone + Atrasentan	Endothelin A receptor antagonist	PFS	NCT00134056
Docetaxel/Prednisone + ZD4054	Endothelin A receptor antagonist	OS	NCT00626548
Docetaxel/Prednisone + Bevacizumab	VEGF blocking monoclonal antibody	OS	NCT00110214
Docetaxel/Prednisone + Aflibercept (VENICE)	Soluble decoy receptor for VEGF	OS	NCT00519285
ZD4054 (ENTHUSE M0; ENTHUSE M1)	Endothelin A receptor antagonist	OS	NCT00554229 NCT00617669
Abiraterone Acetate + Prednisone	CYP17A1 inhibitor	OS, PFS	NCT00887198

Abbreviations: OS = overall survival; PFS = Progression free survival; and TTF = time to treatment failure.

Table 3. Active phase III trials in first-line chemotherapy for CRPC.

Drug	Mechanism of action	Primary endpoint	Clinical trial Registration number
XRP6258 + Prednisone vs Mitoxantrone + Prednisone	Taxane with a low affinity for P-gp	OS	NCT00417079
Sipuleucel-	T Active cellular immunotherapy	Safety and efficacy	NCT0065442
Abiraterone Acetate + Prednisone	CYP17A1 inhibitor	OS	NCT00638690
MDV3100 (AFFIRM)	AR antagonist	OS	NCT00974311
Ipilimumab	CTLA-4 blocking monoclonal antibody	OS	NCT00861614
Sunitinib + Prednisone	Multitarget Tyrosine Kinase inhibitor	OS	NCT00676650

Abbreviations: OS = overall survival.

Table 4. Active phase III trials in second-line chemotherapy for CRPC.

5. Newer chemotherapy

New chemotherapeutic agents that are less susceptible to the mechanisms that give rise to taxane resistance in CRPC are urgently needed. Of the novel chemotherapeutic agents, the epothilone analog class (Figure 5) is of particular interest.

5.1 Epothilones

The epothilones are microtubule stabilizing agents that initiate apoptosis in cancer cells by disrupting the dynamic characteristics of microtubules [68]. The epothilones (Figure 5) include natural epothilone B (EPO906; patupilone; Novartis, Basel, Switzerland) and several semisynthetic epothilone compounds such as BMS-247550 (ixabepilone; aza-epothilone B; IXEMPRA; Bristol-Myers Squibb, New York, NY) and sagopilone (ZK-EPO; Schering AG, Berlin, Germany). Ixabepilone is the first of these agents to receive FDA approval for use in the treatment of metastatic or locally advanced breast cancer in combination with capecitabine after failure of an anthracycline and a taxane, or as monotherapy after failure of an anthracycline, a taxane, and capecitabine.

The epothilones induce cell cycle arrest at the G2/M phase via tubulin polymerization [69]. However, epothilones and taxanes have important differences in modes of binding and the sites of binding to tubulins [70]; ixabepilone has been shown to affect multiple β-tubulin isoforms. It suppresses the dynamic instability of class III β-tubulin and class II β-tubulin microtubules, whereas taxanes are not known to bind to class III β-tubulin [71, 72]. It has also been shown that the tubulin polymerizing activity of epothilone B is approximately 2- to 10-fold greater than that of the commonly used taxane- paclitaxel [73].

The epothilones appear to be less susceptible to classic tumor resistance mechanisms such as P-gp or MRP efflux, tubulin mutations, and alterations in tubulin isotypes [74, 75]. It has been quite well documented that epothilones are more efficacious in taxane-resistant cell lines and xenografts [76, 77]. There is no evidence of cross-resistance between taxanes and epothilones which is another justification for their potential use to tackle taxane resistance [78].

5.1.1 Clinical activity of epothilones

Epothilones have been tested as first-line (against chemo-naïve tumors), second-line (against tumors previously treated with chemotherapy) or third-line (against tumors previously treated with 2 types of chemotherapy). Some of the important clinical trials are described below.

First-line therapy: In a multi-institutional, randomized, phase II study in chemotherapy-naïve patients, Galsky and colleagues [79] showed that ixabepilone was active in the treatment of CRPC, irrespective of the addition of the well established chemotherapeutic-estramustine. PSA declines of > 50% were reported in 31/45 patients (69%) in the combination arm and 21/44 patients (48%) in the ixabepilone monotherapy arm. Median progression-free survival (PFS) was 5.2 months and 4.4 months in the combination and monotherapy arms, respectively. The most important side effect of ixabepilone was neutropenia.

The Southwest Oncology Group trial SO111 extended these results in a study of 42 patients with metastatic CRPC treated with ixabepilone 40 mg/m^2 [80]. Fourteen patients (33%) achieved a PSA response (the definition of which required at least stable measurable disease), with the majority (72%) achieving a reduction > 80%. Median PFS was 6 months and median overall survival was 18 months.

In the pilot study reported by Smaletz and colleagues [81] they examined the efficacy of intravenous ixabepilone in combination with oral estramustine (280 mg 3x daily on days 1 to 5) in 13 chemotherapy-naïve patients with CRPC. The reported decline in PSA levels > 50% was in 11 patients (92%), out of which 5 patients achieved reductions in excess of 80%. Among the 7 patients with measurable disease, there was 1 complete response (CR) and 3 partial responses (PRs), and an additional patient achieved disease stabilization. The most common adverse events was neutropenia reported in 4 patients.

Second-line therapy: The utility of ixabepilone as a second-line agent in patients previously treated with a taxane has also been evaluated [78]. A phase II randomized study compared ixabepilone 35 mg/m^2 every 3 weeks with intravenous mitoxantrone 14 mg/m^2 every 3 weeks plus prednisone 5 mg twice daily in 82 patients with taxane refractory CRPC [78]. PSA declines > 50% were reported in 17% of patients treated with ixabepilone and 20% of those treated with mitoxantrone plus prednisone. In patients with measurable disease, the objective response rate (ORR) was 7% and 6%, respectively.

To sum up, epothilones represent a very effective option to treat taxane resistant CRPC.

6. Endothelin receptor antagonists

Endothelins are regulators of cell vasomotor tone, and angiogenesis. The endothelins bind to two receptors, endothelin-A and endothelin-B, and play a major role in tumor growth, proliferation, angiogenesis, and bone metastasis [82]. Several studies have shown that patients with metastatic prostate cancer have elevated levels of plasma endothelin-A

compared with patients with localized cancer. Endothelin-A is also thought to promote osteoblastic activity characteristic of bone metastases in prostate cancer [83].

Atrasentan (**Figure 5**) is mainly an endothelin-A receptor antagonist. In a phase II, randomized, double-blind trial on patients with metastatic CRPC, 288 asymptomatic patients received either placebo or once-daily atrasentan, 2.5 or 10 mg [4]. The 10 mg atrasentan group had a longer median TTP (time to progression) (187 *vs.* 137 days for the placebo group, P = 0.02). Median time to PSA progression was 155 days for the atresantan 10 mg group compared with 71 days for the placebo group (P = 0.002). Headaches were the main reversible side effect. Encouraging results from this trial led to phase III investigations. In a phase III multicenter trial, 809 men with CRPC were randomized in a 1:1 fashion to atrasentan 10 mg daily *vs.* placebo [4]. The primary endpoints were TTP assessed radiographically and clinically. Atrasentan did not reduce TTP relative to the placebo arm (hazard ratio 0.89, P = 0.136). In an exploratory analysis, however, bone alkaline phosphatase and PSA levels were significantly lower in the atrasentan arm (P<0.05). In a second phase III trial, 941 men with PSA-only CRPC were randomized to receive atrasentan 10 mg daily *vs.* placebo [83]. Fewer men treated with atrasentan (227) experienced disease progression compared with placebo (267), and the median survival was longer for the atrasentan group (P = 0.176), however, this longer median survival was not statistically not significant. PSA doubling time prolongation and a decrease in alkaline phosphatase were seen in the treatment group (P = 0.031 and P = 0.001, respectively). although atrasentan did not meet the primary endpoint expectations, it did have an impact on molecular markers that indicate disease progression. Hence, Southwest Oncology Group is currently conducting a phase III trial investigating docetaxel with or without atrasentan in men with metastatic CRPC.

7. Antisense oligonucleotides

Antisense oligonucleotides (ASOs) offer a novel approach to regulate genes involved in cancer progression, especially those that are not targetable by drugs [84]. ASOs are single-stranded, chemically modified DNA-like molecules that are 15–25 nucleotides in length. They are designed to be complementary to a selected gene's mRNA and thereby specifically inhibit expression of that gene. It is estimated that any sequence of at least 13 bases in RNA and 17 bases in DNA is represented only once within the human genome. Thus, the specificity involved in the design of ASOs theoretically leads to decreased toxicity. There has been tremendous development in the ASO technology in this decade. However, there are several challenges that need to be addressed such as optimization of ASO's tissue exposure, cellular uptake and demonstration of mechanism of action and antitumour activity.

The clusterin gene encodes a cytoprotective chaperone protein which has been implicated in a number of physiologic processes [85]. During times of stress, it is thought to act as a survival protein and stabilizes conformations of proteins [86]. In prostate cancer, increased clusterin levels are in direct linear relationship with Gleason score [17]. Although clusterin expression is low in most untreated hormone-naÏve tissues, levels increase significantly within weeks after neo-adjuvant hormone therapy [87]. Preclinical studies have indicated that clusterin suppresses apoptotic cell death in response to androgen withdrawal and chemotherapy, [88, 89]. OGX-011 (OncoGeneX Technologies, Vancouver, British Columbia, Canada) is a second-generation ASO against the human clusterin mRNA. OGX-011 incorporates 2'-O-methoxyethyl modifications to the four bases on either end of the 21-mer

phosphorothioate backbone [89]. Such modifications maintain the improved tissue pharmacokinetic profile and relaxed dosing regimen but preserve the high affinity for target mRNA and the recruitment of RNase H necessary for target degradation.

In a randomized phase II trial, CRPC patients who relapsed at or within 6 months of first-line docetaxel were treated with custirsen in combination with either docetaxel or mitoxantrone in a second-line setting [90]. In both arms, efficacy was reported but the docetaxel/custirsen arm appeared to be superior to the mitoxantrone/custirsen arm with respect to PSA response (40% *vs.* 27%), pain response (8/12 *vs.* 6/12), PFS (7.5 months *vs.* 4.2 months), and safety. Median survival duration had not been reached in both arms at a median follow-up of 13.3 months.

In another phase II randomized study [91], patients were randomly assigned 1:1 to receive docetaxel/prednisone either with (arm A) or without (arm B) OGX-011 640 mg intravenously weekly. The primary end point was the proportion of patients with a prostate-specific antigen (PSA) decline of ≥ 50% from baseline, with the experimental therapy being considered of interest if the proportion of patients with a PSA decline was more than 60%. Secondary end points were objective response rate, progression-free survival (PFS), overall survival (OS), and changes in serum clusterin. Eighty-two patients were accrued, 41 to each arm. OGX-011 adverse effects included rigors and fevers. After cycle 1, median serum clusterin decreased by 26% in arm A and increased by 0.9% in arm B ($P < .001$). PSA declined by ≥ 50% in 58% of patients in arm A and 54% in arm B. Partial response occurred in 19% and 25% of patients in arms A and B, respectively. Median PFS and OS times were 7.3 months (95% CI, 5.3 to 8.8 months) and 23.8 months (95% CI, 16.2 months to not reached), respectively, in arm A and 6.1 months (95% CI, 3.7 to 8.6 months) and 16.9 months (95% CI, 12.8 to 25.8 months), respectively, in arm B. Baseline factors associated with improved OS on exploratory multivariate analysis were an Eastern Cooperative Oncology Group performance status of 0 (hazard ratio [HR], 0.27; 95% CI, 0.14 to 0.51), presence of bone or lymph node metastases only (HR, 0.45; 95% CI, 0.25 to 0.79), and treatment assignment to OGX-011 (HR, 0.50; 95% CI, 0.29 to 0.87). Two phase III trials in first-line and second-line treatment have been announced recently. Primary end point will be pain palliation (second-line) and OS (first-line). Thus, custirsen is a promising candidate for the second-line treatment of CRPC.

8. Immunotherapy

Suitability of vaccine development in prostate cancer: Prostate cancer has features that are suitable for vaccine development such as the following: the rate of disease progression is slow enough to allow for a month-long immune intervention, and then some latency until it is evident; the organ is biologically "dispensable," providing a theoretical safety margin. There are a variety of response end points—PSA response, time to PSA progression, time to radiologic progression, time to symptomatic progression, or overall survival.

Theoretical susceptibility of the tumor to immune mediated attack is difficult to quantify. Several studies show that tumors modify the capacity of the immune system to attack it. Several intratumoral features show that there is impaired immune attack in peritumoral regions. These mechanisms include class I Human Leukocyte Antigen (HLA) downregulation (corresponding to decreasing susceptibility to CD8 CTL lysis) [92], PD-1 ligand expression [93]. A more indirect effect may be a consequence of local expression of cytokines including vascular endothelial growth factor (VEGF), interleukin 10 (IL-10), tumor

growth factor beta (TGF-β) that induce a tolerogenic phenotype in antigen presenting cells (APC). Other intratumoral escape mechanisms [94] include indoleamine 2,3-dioxygenase [95] and nitric oxide synthetase [96].

8.1 Sipuleucel-T

In April 2010, sipuleucel-T became the first immunotherapeutic agent to be approved by the U.S. Food and Drug Administration for prostate cancer, based on consistent observed improvements in overall survival. Sipuleucel (Provenge, APC8015) contains mature, autologous antigen-presenting cells (APCs). APCs are obtained from the patient via a standard leukapheresis procedure approximately two days before each scheduled infusion. The patient's APCs are co-cultured with a recombinant fusion protein containing prostatic acid phosphatase (PAP). The activated, antigen-loaded APCs are then infused into the patient, where it can potentially stimulate a T cell response against prostate cancer cells. The process is performed three times over the course of a four-week period. The vaccine has been studied in three phase III clinical trials. The first phase III study, D9901, consisting of 127 men with asymptomatic, metastatic CRPC, compared sipuleucel-T every two weeks for three cycles with placebo in a 2:1 ratio [97]. The final three-year follow-up of the D9901 phase III study showed a median survival benefit of 4.5 months and a threefold improvement in survival at 36 months for patients who were randomized to receive Provenge [97]. In another similar phase III trial, D9902, 98 men with asymptomatic, metastatic CRPC demonstrated a 20% improvement in OS for patients randomized to sipuleucel-T. In both studies, the vaccine was well tolerated, and the most common adverse events were fever and chills. The third phase III trial, D9902B, also known as the IMPACT trial (Immunotherapy for Prostate Adenocarcinoma Treatment) was a randomized, double-blind, placebo-controlled study comparing Provenge with placebo in 512 men with CRPC randomized in 2:1 ratio. The results were presented at the 2009 American Urological Association Annual Meeting. The median overall survival favored the vaccine arm with a 4.1-month increase in overall survival for patients treated with sipuleucel-T (25.8 *vs.* 21.7 months; P = 0.032). Also, 31.7 percent of sipuleucel-T patients were alive at three years as compared to 23.0% of placebo patients. The 36-month overall survival was 33% in the sipuleucel-T group and 20% in the placebo group [97]. Sipuleucel-T is the first active immunotherapy to demonstrate an improvement in overall survival for advanced prostate cancer. Given the short duration of the therapy (one month) and its favorable benefit-to-risk ratio, sipuleucel-T provides an attractive new option for the management of advanced prostate cancer. The FDA approval was granted to sipuleucel when confirmatory IMPACT trial found a 22.5% improvement in mortality risk compared to placebo (median survival: 25.8 months *vs.* 21.7 months) [98]. Treatment with sipuleucel-T was well tolerated; the most common complications included mild-to-moderate chills, pyrexia, and headaches, which were transient.

8.2 GVAX

Another immunotherapy in development is GVAX (Cell Genesys, San Francisco, California, USA). Unlike Provenge, GVAX is a cell-based gene-transduced multiantigen vaccine. It was developed using two human prostate cancer cell lines, LNCaP and PC-3. The cells in these vaccines are modified to produce granulocyte macrophage-colony stimulating factor (GM-CSF)-stimulating APC [3, 99]. GVAX was developed with a hypothesis that combining

GM-CSF with the prostate cancer-specific antigens would promote synergy and, thus, a stronger cytotoxic response against prostate cancer cells. GM-CSF has already shown modest activity in advanced prostate cancer [3]. After the vaccine is administered, GVAX is recognized as foreign and engulfed by the APC. Subsequently, APC carry these cells to lymph nodes that are recognized as foreign, stimulating antibody production with activation of CD4+ and CD8+ cells. The first phase III trial (VITAL-1) compared GVAX with Docetaxel and prednisone for 6 months [100]. The second phase III trial (VITAL-2) compared GVAX/Docetaxel with Docetaxel/prednisone. VITAL-2 was terminated in August 2008 because of excessive deaths in the GVAX arm [101]. VITAL-1, which completed accrual, was terminated because of futility analysis indicating that there was less than 30% chance of achieving a survival benefit. Thus, the future development of GVAX remains uncertain.

8.3 Gene therapy

Prostate-specific antigen-expressing poxvirus vaccine (PROSTAVAC) is a form of immunotherapy using poxvirus that has been genetically engineered to carry a human PSA gene and has been transformed into the PROSTAVAC vaccine, stimulating the cytotoxic T cells to attack prostate cancer cells. Several phase I trials have demonstrated activity with this vaccine, and it is fairly well tolerated [102]. A phase II trial demonstrated 45.3% of men with CRPC free of PSA progression at 19.1 m1onths, and 78.1% demonstrated clinical PFS. The analysis of antibody titers revealed no significant increases in anti-PSA antibody; however, it did demonstrate an increase in PSA-reactive T cells [103]. Although promising, these results need to be verified in larger phase III randomized trials.

9. Calcitriol

Calcitriol (1,25-dihydroxycholecalciferol) (**Figure 5**) is the hormonal form of vitamin D3. In unphysiologic concentrations, calcitriol has shown antitumor activity in several *in vitro* and *in vivo* models [104]. Furthermore, its antitumoral activity is synergistic in combination with other cytotoxic agents. After a successful phase II trial with an improvement in OS of up to 24.5 months in the experimental arm with docetaxel and calcitriol, a phase III trial was initiated (ASCENT 2) [4]. In a weekly setting, the combination of docetaxel with calcitriol was compared with docetaxel alone. But this trial was abruptly closed due to a higher death rate in the calcitriol arm. Analysis of clinical data that could explain the causes of deaths have not been reported. Due to these findings and the missing analysis of the ASCENT 2 trial, calcitriol cannot be recommended in CRPC after docetaxel failure.

10. Thalidomide

Thalidomide (**Figure 5**), designed in the 1950s of the 20th century, was used as a sedative and antiemetic against sickness in the first trimester of gestation. Unfortunately, it was accountable for more than 10,000 congenital abnormalities and thus it was withdrawn from the market. It has been shown to inhibit angiogenesis-induced by fibroblast growth factor (FGF) and VEGF. Furthermore, it has immunomodulatory functions. Due to the fact that angiogenesis is an important step in metastasis of any cancer, several trials with use of thalidomide were performed. As a single agent it showed modest PSA responses in a range between 15% and 18% [94, 105]. In a multidrug combination (docetaxel/ estramustine

/thalidomide), however, a PSA decline of 90% (18/20) was observed, one of the highest response rates ever seen in such trials [106]. In a phase I trial, only 2/13 (15%) docetaxel pretreated patients showed PSA declines > 50% when receiving thalidomide in combination with oral daily cyclophosphamide [107]. Another phase I/II trial similar to the study mentioned above was performed in pretreated CRPC. Paclitaxel was used in place of docetaxel. 14 of 38 patients had previous taxane therapy; 9 of these 14 patients (64%) had PSA declines > 50% [108]. In another phase II trial, 39 pretreated CRPC patients, most of whom had prior docetaxel (35/39), received thalidomide and daily oral dexamethasone; 26% (10/39) had PSA declines and no signs of radiologic progression [109]. Currently, there is one active trial in pretreated CRPC (thalidomide + doxorubicin). Briefly, we have some evidence that thalidomide has modest effects in taxane pretreated CRPC However, the clinical data suggests that its effects can be enhanced when it is combined with other cytotoxic agents.

11. Conclusions

The multifaceted problem of CRPC needs a multidisciplinary approach. Many aspects of the disease need to be taken into account when deciding on treatment. Relatively few therapy options exist for patients with prostate cancer that has become resistant to ADT and has metastasized to distant sites. Survival of such patients is poor, with a median survival time of 20 months from the time of initiation of standard docetaxel-based chemotherapy. Over the last decade, our understanding of the pathogenesis of prostate cancer, including the molecular basis of androgen resistance and other regulatory pathways, has been advancing. This advancement has further led to more novel agents that specifically target these molecular pathways in the treatment of CRPC. When prostate cancer progresses following ADT, there are currently few treatment options with only docetaxel shown to prolong life as indicated by TAX-327 and SWOG studies. The introduction of docetaxel for the treatment of CRPC came along with advances in OS and quality of life. Nevertheless, referring to a prolongation of survival of approximately 3 months in a phase III trial, its overall benefit constitutes only a small step in this challenging field.

Approaches in fundamental research are providing us with understanding of more and more the mechanisms of carcinogenesis. As a result of this advancement, the targeted drugs take a major place in the treatment of several cancer entities. The use of a targeted drug as a single-agent often demonstrated only weak or no efficacy. The problem in their use is that tumor cells exhibit plasticity in signaling pathways. Plasticity means that inhibition of one pathway may lead to up-regulation of parallel pathways or that inhibition of an upstream pathway is unable to down-regulate an overactive and uncoupled downstream pathway. Recently, several promising approaches yielded disappointing results in the phase III setting (GVAX, calcitriol); nonetheless, expectations for other agents (Abiraterone, VN/124-1 (TOK-001), Atrasentan, Provenge) still remain high. These agents will need to demonstrate survival benefit for approval. Due to the rapid progress of this field it is beyond the scope of this review to cover all compounds under investigation. However, we have focused on several broad therapeutic categories and selected targets with significant biologic rationale and a reasonable likelihood of success in this review. We sincerely hope that this chapter will add immensely to our knowledge about the current and emerging therapies to fight prostate cancer.

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13. Disclosure of potential conflicts of interest

Professor. Vincent C. O. Njar is a co-inventor on patents and patent applications covering VN/124-1 (TOK-001) and related compounds and serves as consultant for Tokai pharmaceuticals Inc. No writing assistance was utilized in the production of this manuscript.

14. Note added in proof

Abiraterone acetate (ZYTIGA™) was recently (April 28, 2011) approved by the US Food and Drug Administration (FDA) for the treatment of men with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

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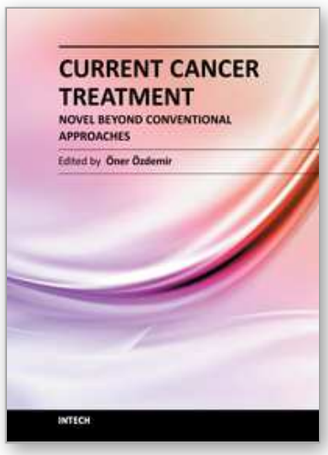

Current Cancer Treatment - Novel Beyond Conventional Approaches

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Currently there have been many armamentaria to be used in cancer treatment. This indeed indicates that the final treatment has not yet been found. It seems this will take a long period of time to achieve. Thus, cancer treatment in general still seems to need new and more effective approaches. The book "Current Cancer Treatment - Novel Beyond Conventional Approaches", consisting of 33 chapters, will help get us physicians as well as patients enlightened with new research and developments in this area. This book is a valuable contribution to this area mentioning various modalities in cancer treatment such as some rare classic treatment approaches: treatment of metastatic liver disease of colorectal origin, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer; new therapeutic approaches of old techniques: laser-driven radiation therapy, laser photo-chemotherapy, new approaches targeting androgen receptor and many more emerging techniques.

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