Review Article
Drug resistance in castration resistant prostate cancer: resistance mechanisms and emerging treatment strategies

Cameron M Armstrong¹, Allen C Gao¹,²

¹Department of Urology, ²Comprehensive Cancer Center, University of California at Davis, Sacramento, CA, USA

Abstract: Several mechanisms facilitate the progression of hormone-sensitive prostate cancer to castration-resistant prostate cancer (CRPC). At present, the approved chemotherapies for CRPC include systemic drugs (docetaxel and cabazitaxel) and agents that target androgen signaling, including enzalutamide and abiraterone. While up to 30% of patients have primary resistance to these treatments, each of these drugs confers a significant survival benefit for many. Over time, however, all patients inevitably develop resistance to treatment and their disease will continue to progress. Several key mechanisms have been identified that give rise to drug resistance. Expression of constitutively active variants of the androgen receptor, such as AR-V7, intracrine androgens and overexpression of androgen synthesis enzymes like AKR1C3, and increased drug efflux through ABCB1 are just some of the many discovered mechanisms of drug resistance. Treatment strategies are being developed to target these pathways and reintroduce drug sensitivity. Niclosamide has been discovered to reduce AR-V7 activity and synergized to enzalutamide. Indomethacin has been explored to inhibit AKR1C3 activity and showed to be able to reverse resistance to enzalutamide. ABCB1 transport activity can be mitigated by the phytochemical apigenin and by antiandrogens such as bicalutamide, with each improving cellular response to chemotherapeutics. By better understanding the mechanisms by which drug resistance develops improved treatment strategies will be made possible. Herein, we review the existing knowledge of CRPC therapies and resistance mechanisms as well as methods that have been identified which may improve drug sensitivity.

Keywords: Drug resistance, castration resistant, prostate cancer, treatment strategies

Introduction
Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer related deaths in men; attributing to over 29,000 deaths in 2014 in the United States alone [1, 2]. Additionally, 14% of all newly diagnosed cancers in the United States are prostate cancer and 15% of men will be diagnosed with this disease in their lifetime [3]. Initial treatments for prostate cancer focus on the use of androgen deprivation therapies (ADT) to reduce levels of circulating androgens in order to stop tumor growth. ADT is achieved either surgically via bilateral orchiectomy to inhibit androgen synthesis by the testes or with medical castration using drugs including gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, and anti-androgens to reduce circulating levels of androgen and reduce androgen receptor (AR) activation. Unfortunately, after 2-3 years of ADT, patient’s often progress to castration-resistant prostate cancer (CRPC) at which point therapeutic choices are limited but continuously being improved upon [4].

CRPC, previously hormone-resistant prostate cancer, is defined as progression of disease in the presence of castrate levels of circulating testosterone [5, 6]. It is hallmarkmed by hyper-activation and/or overexpression of the AR resulting in the transcription of downstream target genes and tumor progression despite only castrate levels of androgen being present in the patient. Dysregulated mechanisms that contribute to the development of CRPC from hormone-sensitive prostate cancer have been extensively investigated and can be broken up into five
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The aim of this review is to outline current methodologies used in the treatment of CRPC with a focus on mechanisms that become dysregulated as prostate cancer patients develop resistance to these chemotherapeutics. Developmental strategies showing promise for overcoming acquired resistance will be highlighted.

Docetaxel and cabazitaxel

Until recently, the primary treatment for CRPC has been docetaxel since it was approved in 2004 however newer drugs such as enzalutamide and abiraterone have overtaken its use as the first-line treatment. Data from the CHAARTED trial, however, demonstrate that docetaxel as an initial treatment for hormone-naive prostate cancer in conjunction with ADT in patients with high volume or visceral metastases provided a 17-month survival advantage over androgen ablation [14].

Docetaxel is an anti-mitotic chemotherapeutic used for the treatment of several other varieties of cancer including cancers of the breast,

Figure 1. An overview of approved and experimental treatment strategies for CRPC targeting the androgen axis. Currently approved therapies are written in red while experimental therapies are in orange.
lung, and stomach. In the treatment of prostate cancer, docetaxel is often used in combination with prednisone and functions by binding to free tubulin within cells promoting the formation of stable microtubules preventing depolymerization which results in inhibition of mitosis and consequent induction of apoptosis [15-17]. Furthermore, docetaxel has been shown to reduce AR expression in CRPC cells [18].

Cabazitaxel is a newer FDA approved taxane used for the treatment of CRPC in patients who have failed docetaxel chemotherapy. Compared to mitoxantrone, the TROPIC clinical trial observed cabazitaxel to have a 2.4 month survival benefit in patients with metastatic CRPC whose disease had progressed on docetaxel [19]. While both taxanes function through tubulin binding, cabazitaxel has unique mechanisms of action and therefore resistance compared to docetaxel [20]. Unlike docetaxel, cabazitaxel has low affinity for the MDRP ABCB1, a fact that led to its selection as a chemotherapy [21, 22].

**Docetaxel resistance**

Resistance to docetaxel treatment is well characterized and arises due to a number of different mechanisms. Many of these mechanisms are related to aberrant regulation of molecules involved in cell survival and death. Overexpression or activation of signal transducers and activator of transcription (Stat) 1, Stat3, clusterin, heat shock proteins (HSP), and nuclear factor kappa B (NF-κB), among others, are associated with docetaxel resistance [23-28]. Furthermore, Vidal et al. observed that GATA2 upregulation and the resultant increase in IGF2 and activation of downstream targets promoted docetaxel resistance in murine models [29]. Conversely, reduced activity or expression of wild type p53 is linked to insensitivity to docetaxel [30].

Overexpression of inflammation associated molecules has also been demonstrated to cause resistance to docetaxel. Interleukin (IL) 6 enhances proliferation and inhibits apoptosis of prostate cancer cells. Secretion of this cytokine is inversely correlated to docetaxel response in CRPC patients, and increased IL-6 is due in part to increased levels of NF-κB [24, 31]. Similarly, increased expression levels of IL-8, chemokine ligand 2 (CCL2), transforming growth factor-β1 (TGF-β1) and macrophage inhibitory cytokine-1 (MIC-1) have all been tied to promoting docetaxel resistance [32-36].

Increased expression of β-tubulin isoforms has also been linked to docetaxel resistance. In particular, taxanes have reduced efficiency for binding to the class III β-tubulin isoform [37, 38]. Studies have also found increased expression of class IV β-tubulin and mutations to class 1 β-tubulin causing impaired polymerization in docetaxel resistant cells [39, 40].

Another class of molecules dysregulated in docetaxel resistance is multidrug resistance proteins (MDRP). MDRP, such as P-glycoprotein, function as pumps to excrete drugs, including docetaxel, into the extracellular fluid. This reduces the drugs ability to target cells and leads to drug resistance. In vitro analyses of docetaxel-resistant cells have revealed that overexpression and phosphorylation of breast cancer resistance protein (BCRP) induces docetaxel resistance [41]. Additionally, expression of P-glycoprotein (P-gp, MDR1 or ABCB1) is significantly increased in docetaxel-resistant compared to docetaxel-sensitive DU145, CWR22RV1 and C4-2B parental cell lines [27, 42].

Thadani-Mulero et al. observed that androgen receptor splice variants (which will be discussed in further detail later) can influence sensitivity to docetaxel. They found that the AR variant ARV-567 was sensitive to microtubule stabilization induced by taxanes whereas AR-V7 was unaffected. Furthermore, AR-V7 expressing tumor xenografts were resistant to docetaxel therapy while ARV-567 expressing xenografts where highly sensitive to docetaxel [43].

**Overcoming docetaxel resistance**

A number of experimental strategies have been explored for reintroducing docetaxel sensitivity. Unfortunately, while many methods have been effective in in vitro and in vivo models, clinical data to support these findings are either lacking or have shown little efficacy in later phase prostate cancer trials. One line of attack is to mediate expression of up-regulated pro-survival and pro-inflammatory molecules found to be associated with increased resistance. Inhibition of NF-κB with BAY 11-7082 in docetaxel resis-
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tant cell lines resulted in re-sensitization of these cells to docetaxel treatment [27]. Niu et al. found that the natural anti-inflammatory compound Marchantin M, found in liverwort plants, was capable of reducing IL-6 and TNFα expression and inactivating NF-κB and resulted in increased docetaxel sensitivity in prostate cancer cells [44]. Furthermore, inhibition of IGFI1R expression, a molecule involved in the GATA2-IGF2 signaling axis, using the selective IGFI1R/INSR inhibitor OSI-906 was observed to improve both docetaxel and cabazitaxel sensitivity in resistant cell lines [29].

Targeting ABCB1 efflux pathways and β-tubulin isoforms are two other methods researchers have investigated for resensitizing cells to docetaxel. To this effect, phase I and II clinical trials have investigated the efficacy for using MDRP inhibiting drugs, such as elacridar, in combination with chemotherapy. While phase I trials showed promise, only minimal clinical activity was observed in phase II trials [45, 46]. Interestingly, Zhu et al. observed that treatment of docetaxel resistant C4-2B cells with the dietary flavone apigenin overcomes ABCB1 mediated docetaxel resistance and resensitizes cells to drug treatment by inhibiting ABCB1 expression and likely reducing drug efflux [42]. ABCB1 efflux activity was also found to be inhibited by the anti-androgens enzalutamide and bicalutamide. Co-treatment with bicalutamide and docetaxel in both AR-positive and AR-negative docetaxel resistant mouse xenograft models was observed to significantly reduce tumor growth, suggesting that this effect is independent of AR status [47]. In regards to β-tubulin, the synthetic estrogen diethylstilbestrol has been demonstrated to suppress expression of β-tubulin isoform IVa and was observed to enhance tumor growth inhibition in combination with docetaxel in prostate cancer xenograft models [48]. Other groups have found that the N-terminal domain of the AR interacts with tubulin [49]. Targeting this domain with the small-molecule inhibitor EPI in conjunction with docetaxel therapy improved docetaxel effectiveness and reduced the number of cells displaying the epithelial-mesenchymal-transition (EMT) phenotype [50].

The use of nanoparticles for docetaxel delivery into cells has also been associated with improved docetaxel sensitivity. Several classes of nanoparticles have been developed, including liposomes, polymeric micelles, and nanoconjugates. The overarching goals of using these particles are to increase specificity for cancer cells, and improve drug retention and absorption while reducing non-specific toxicity in the patient. The use of nanoparticles has been found to reduce docetaxel efflux, either by avoiding efflux or by inhibiting increased expression of MDRP observed in the presence of free docetaxel [51-53]. Additionally, compared to free docetaxel, magneto-liposome bound docetaxel has been shown to inhibit activation of receptor tyrosine kinase pathways including EGFR, PI3K and Erk1/2 mediated MAP kinase, suggesting that the bound drug has improved anti-proliferative efficacy and renders cells more sensitive to treatment [54]. The majority of these studies, however, has been conducted in cancer models other than prostate cancer and serve as proof-of-principle for nanoparticle action in prostate cancer docetaxel resistance.

Cabazitaxel resistance

Due to its more recent emergence as a chemotherapeutic in CRPC, less is known about the development of cabazitaxel resistance compared to other drugs. Similarly to docetaxel, interfering with tubulin expression can influence cabazitaxel sensitivity. Specifically, Galletti et al. found that ETS-related gene (ERG) overexpression in prostate cells leads to cabazitaxel resistance both in vitro and in vivo [55]. They determined that cytoplasmic expression of ERG interacts with β-tubulin and tubulin dimers and that interruption of this interaction restores cabazitaxel sensitivity. Other studies investigating cabazitaxel resistance have found that CRPC tumors expressing low levels of retinoblastoma had improved cabazitaxel response [20].

Anti-androgens

Abiraterone acetate

Unlike docetaxel and cabazitaxel, abiraterone acetate (Zytiga) functions as an anti-androgen. Progression to CRPC includes the ability of prostate cancer cells to utilize the 5α-dione pathway to bypass testosterone in the steroidogenesis pathway, leading to production of dihydrotestosterone (DHT). Despite this, CRPC cells
still rely on adrenal androgens which get converted to androstenedione by 3βHSD in the prostate or adrenal gland. DHT is then formed from the androstenedione. Abiraterone works by preventing the formation of androgen precursors required for androgen production in prostate tumors. Specifically, abiraterone reduces circulating androgen levels by inhibiting CYP17A1. Inhibition of CYP17A1 blocks the conversion of pregnenolone to DHT resulting in significant loss of androgen production in peripheral tissues and loss of production of precursors needed for intratumoral androgen synthesis. Recent studies suggest that the potency of abiraterone is increased by conversion to the more active Δ4-abiraterone (D4A) and that this D4A is responsible in part for the clinical activity of abiraterone. In vivo and clinical data demonstrate the conversion of abiraterone to D4A and further show that D4A inhibits CYP17A1, 3βHSD and SRD5A. Additionally, D4A was shown to have improved inhibition of tumor xenograft growth compared to abiraterone [56].

In patients who had progressed after docetaxel therapy, the phase III trial COU-AA-301 demonstrated a 3.9 month survival benefit of abiraterone/prednisone over placebo/prednisone and the subsequent COU-AA-302 trial showed a 4.4 month survival benefit with abiraterone in chemotherapy-naive CRPC patients [12, 57, 58]. Unfortunately, one-third of all patients display primary resistance to abiraterone treatment, and all patients with initial response progressed by 15 months of abiraterone chemotherapy [12].

**Abiraterone resistance**

Resistance to abiraterone in patients is tied to re-activation of androgen synthesis in prostate cancer cells. Up-regulation of and mutations to enzymes involved in the steroidogenesis pathway are likely contributors to both CRPC progression and abiraterone resistance. Mostaghel et al. detected a 1.3-4.5 fold increase in enzymes involved in steroidogenesis in abiraterone treated LuCaP cell lines, including CYP17A1, AKR1C3, HSD17B3, and SDR5A2 [59]. Additionally, Chang et al. observed the 1245C mutation in HSD3B2 in abiraterone-resistant xenograft models [60]. IL-6 has also been identified as a mediator of increased expression of steroidogenic enzymes, including HSD3B2 and AKR1C3 [61]. AKR1C3 in particular is an important enzyme in the steroidogenesis pathway. Its activation contributes to CRPC drug resistance in patients treated with both abiraterone and enzalutamide and it has been suggested as a biomarker for assessing prostate cancer progression [62, 63].

In addition to alterations in steroidogenesis, AR activation by ligands other than androgen may also play a role in abiraterone resistance. Glucocorticoids are often used to reduce side effects associated with abiraterone treatment, however this group of compounds has been demonstrated to activate mutated AR and instigate androgen-independent growth of prostate cancer cells [64]. Furthermore, androgen precursors have been found to accumulate with abiraterone treatment and some of these have been identified to bind mutated AR and instigate downstream signaling [65-67].

**Enzalutamide**

Similar to abiraterone, enzalutamide (Xtandi, ENZA, MDV-3100) also functions by reducing AR activity, albeit via a separate mechanism. Enzalutamide is a competitive inhibitor of ligand binding to the AR. Additionally, it inhibits AR translocation to the nucleus, co-activator recruitment, AR binding to DNA and activation of AR target genes [68]. Enzalutamide has greater affinity for the AR compared to earlier anti-androgens, such as bicalutamide and flutamide, and is subsequently more effective than its predecessors. Data from the AFFIRM trial demonstrated that enzalutamide treated CRPC patients who failed docetaxel treatment had nearly 5 months improved survival compared to placebo treated individuals [13]. Furthermore, the PREVAIL trial found the enzalutamide was also effective in pre-chemotherapy hormone-naïve prostate cancer patients [69]. Primary resistance to enzalutamide was observed in 25% of patients in the AFFIRM trial in whom progression occurred within 3 months of treatment and by 24 months, all patients had progressed in their disease despite enzalutamide therapy [70].

**Enzalutamide resistance**

As cells develop enzalutamide resistance, several key dysregulated mechanisms have been brought to light. Among these are alterations in
steroidogenesis, glucose metabolism, and autophagy. Specifically, Liu et al. observed enzalutamide resistant prostate cancer cells had upregulated expression of androgen and its precursors including cholesterol, DHEA and progesterone. Additionally, this study found that genes involved in steroid biosynthesis where significantly over-expressed compared to enzalutamide-sensitive parental cells and that of these AKR1C3 proved to be of particular importance being as overexpression of this enzyme alone was sufficient to desensitize normally responsive cells to enzalutamide treatment [63].

Point mutations to the AR in the regions coding for the ligand binding domain are also implicated in enzalutamide resistance and it is estimated that 10-30% of CRPC patients have AR mutations [71]. Many of these mutations result in gain-of-function that increase coactivator improvement, alter ligand specificity and affinity. Interestingly, some of these mutations instigate ligand binding specificity to switch from agonist to antagonist activation. In particular, the Phe876Leu mutation in the AR has been associated with enzalutamide activating the AR however further study into this mutation is required to determine clinical significance [72,73].

Other molecular pathways have also been tied to enzalutamide resistance. Studies have determined that overexpression of p52 confers enzalutamide resistance and that this may be due in part to changes in glucose metabolism and expression of AR splice variants, which will be discussed shortly [74-76]. Others have observed that constitutive Stat3 activation due to IL-6 overexpression also induces insensitivity to enzalutamide [77].

**AR splice variants**

AR variants are truncated versions of the wild type AR and are often ligand-independent and constitutively active. AR variants may be generated by genome rearrangement and alternative splicing involving splicing factors such as hRN-PAs [78,79]. Generally, the C-terminal ligand-binding domain is the portion of the AR that is lost, however at least one variant is known to be truncated at the N-terminus resulting in a loss of the DNA binding domain [80-84]. The functional implications of AR variants are not yet fully understood, due in part to the lack of variant specific antibodies, and the role of these variants in CRPC is still being established. CWR22Rv1 cells in have nearly equal expression of full length AR and AR variants however most CRPC cell lines exhibit AR variant expression at some level. Additionally, bone metastases have higher AR variant expression compared to hormone-sensitive prostate cancer and AR variant expression is associated with poorer prognosis and the development of CRPC [85].

Both abiraterone and enzalutamide resistance have been tied to expression AR splice variants [76,86,87]. Among the identified splice variants, variant 7 (AR-V7) in particular has been implicated in drug resistance. Antonarakis et al. demonstrated that AR-V7 expression in patients treated with enzalutamide or abiraterone correlated to a significantly lower PSA response, shorter progression-free and overall survival compared to men without AR-V7 [88]. No changes in PSA response or progression-free survival were observed in patients treated with docetaxel regardless of AR-V7 expression suggesting that AR-V7 positive patients may be less susceptible to primary taxane drug resistance [89].

**Overcoming abiraterone and enzalutamide resistance**

Proposed methods for reintroducing sensitivity to abiraterone and enzalutamide include mediating dysregulated pathways and avoiding AR activation. Liu et al. found that inhibition of AKR1C3 enzymatic activity with indomethacin, a nonsteroidal anti-inflammatory drug, restored enzalutamide sensitivity in resistant prostate cancer cells and suggests that targeting intracrine androgens improves enzalutamide therapy [63]. In a separate study, enzalutamide sensitivity was also restored by inhibiting Stat3 activity using both siRNA and the Stat3 inhibitor AG490 resulting in increased apoptosis and inhibition of prostate cancer cell growth [77]. Others have demonstrated that cells can be resensitized to enzalutamide treatment when administered together with autophagy inhibitors: co-treatment of resistant CRPC cells with enzalutamide and either metformin or clomipramine had greater effect on reducing tumor volume compared to enzalutamide alone in murine models [90]. This has led to the approv-
al for ongoing clinical trials investigating the combinatory effects of metformin with enzalutamide in CRPC patients.

Targeting AR variant expression is effective at reintroducing drug sensitivity and decreasing CRPC tumor growth. The FDA approved antihelminthic drug, niclosamide, has been identified as an AR-V7 inhibitor via several mechanisms including increased AR-V7 protein degradation and reduced recruitment of AR-V7 to promoter regions of target genes resulting in reduced transcriptional activity. The AR-V7 degradation induced by niclosamide was determined to be the result of proteasome-dependent pathways due to the fact that MG132, a 26S proteasome inhibitor, reduced niclosamide-mediated inhibition of AR-V7 protein expression. Furthermore, enzalutamide resistant C4-2B cells expressing AR-V7 displayed a significant dose-dependent cytotoxic effect to niclosamide and when used in combination with enzalutamide had an additive response [91]. On top of its action as an AR-V7 inhibitor, niclosamide has been determined to improve enzalutamide sensitivity by modulating Stat3 activity by inhibiting its phosphorylation and reducing Stat3 target gene expression and abrogating recruitment of AR to the PSA promoter [92]. A recent study by Nadiminty et al. also tied AR-V7 downregulation to enzalutamide resensitization; by downregulating the splice factor hnRNPA1, they were able to decrease AR-V7 expression which sensitized resistant cells to enzalutamide treatment [79]. Another drug, ASC-J9, was found to degrade of both full length and AR-V3 by and associated with a decrease in CWR22Rv1 xenograft tumor growth [93].

While AR-V7 lacks the ligand binding domain, it and other constitutively active variants of the AR retain the N-terminus. Drugs have been developed that target this region of the AR, including EPI and derivatives thereof, and these too have been observed to inhibit prostate cancer cell growth. EPI is known to covalently bind the N-terminal domain of both AR and its variants and inhibit transcriptional activity. In vivo administration of EPI in prostate cancer xenograft models was observed to reduce tumor growth [94, 95]. Niphatenones are another class of drugs that target the N-terminal domain of the AR. While niphatenone treatment was found to inhibit transactivation of AR and its variants, it was also observed to promote glutathione adduct formation and therefore may not be as viable for prostate cancer therapy as alternatives [96].

In addition to therapies aiming to improve the efficacy of existing drugs, novel agents are also being developed and investigated. Drug-seq technology screens genome-wide binding of potential therapeautic agents in various physiological conditions to identify probable therapeautic benefits. This technique identified SD-70, a synthetic chemical, as an inhibitor of prostate cancer translocation and it has further been determined to have in vitro cytotoxic effect on hormone-sensitive LNCaP cells, C42B and drug-resistant C42B cells, and in vivo efficacy in a CWR22Rv1 mouse xenograft model [97].

Cross resistance

With the increase in available chemotherapeutics, cross-resistance has become evident and limits the effective agents in patients who have failed prior therapy. Cross-resistance does not seem to be limited to one class of therapeutics but rather involves all approved CRPC treatments. In a study observing 310 patients with metastatic CRPC, Cheng et al. observed that prior exposure to abiraterone or docetaxel had reduced response to subsequent enzalutamide treatment. Additionally, PSA decline and PSA progression-free survival were diminished in patients previously treated with abiraterone or, to a lesser degree, docetaxel [98]. Other groups have observed similar trends in patients treated with docetaxel following abiraterone treatment and in those receiving enzalutamide post-docetaxel [99-101]. Interestingly, cabazitaxel appears to have less cross-resistance with AR targeted therapies than docetaxel [102, 103]. This may be due to the innate differences in mechanisms of action between these two taxanes including the higher affinity of docetaxel for MDRP and the increased impact of cabazitaxel on cell cycle pathways and chromatin organization [20]. The reduction in docetaxel efficiency observed following AR targeted therapies suggests that taxane therapy may have a role in AR axis modulation. It is important to note, however, that this cross-resistance occurs regardless of the order in which docetaxel and AR targeted therapies are administered.
The emergence of cross-resistance in prostate cancer highlights the necessity for identifying molecules that inhibit resistance pathways that can be used as co-treatments with existing therapies to improve clinical outcome.

Conclusion

CRPC is a complex disease characterized by progression despite the availability of multiple currently approved therapies targeting different pathways. Chemoresistance to these drugs develops over time through a multitude of dysregulated pathways and aberrant AR activation. Intense, ongoing research is dedicated to discerning these pathways and ways to target them to improve drug sensitivity. The more complete understanding of these mechanisms of resistance will enable the development of improved treatment strategies to overcome this resistance.

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Address correspondence to: Allen C Gao, Department of Urology, University of California Davis Medical Center, 4645 2nd Ave, Research III, Suite 1300, Sacramento, CA 95817, USA. E-mail: acgao@ucdavis.edu

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