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INVITED REVIEW

Prostate Cancer

Impact of taxanes on androgen receptor signaling

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The development and progression of metastatic castration-resistant prostate cancer is the major challenge in the treatment of advanced prostate cancer. The androgen receptor signaling pathway remains active in metastatic castration-resistant prostate cancer. Docetaxel and cabazitaxel are the first- and second-line chemotherapy, respectively, for patients with metastatic castration-resistant prostate cancer. These two taxanes, in general, function by (i) inhibiting mitosis and inducing apoptosis and (ii) preventing microtubule-dependent cargo trafficking. In prostate cancer, taxanes have been reported to inhibit the nuclear translocation and activity of the androgen receptor. However, whether this is attainable or not clinically remains controversial. In this review, we will provide a comprehensive view of the effects of taxanes on androgen receptor signaling in prostate cancer.

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) is the major cause of prostate cancer mortality, and taxanes, including docetaxel and cabazitaxel, are the only chemotherapeutic agents proven to provide a survival benefit in patients with mCRPC.[1–3] Docetaxel-based chemotherapy is the first-line treatment and standard of care for patients with mCRPC.[1,4] However, about half of the patients do not respond to the treatment and those do respond become refractory within 1 year.[5] Docetaxel resistance can develop via a number of mechanisms, and overexpression of P-glycoprotein drug efflux pumps to increase the transport of docetaxel out of cancer cells is a common mechanism of resistance.[6] The new taxane cabazitaxel, which has a low affinity to P-glycoprotein,[7] was developed as the second-line chemotherapy for patients with docetaxel resistance.[3,8,9] It prolongs the overall and progression-free survival of mCRPC patients who have failed docetaxel-based therapy.[3]

Taxanes act by binding to beta-tubulin, a major constituent of the microtubule cytoskeleton.[10,11] Microtubules create a scaffold for cell shape and polarization, for transport of cell organelles and vesicles, and for nucleus-cytoplasm trafficking of proteins.[12,13] The best-known function of microtubules is the formation of spindle fibers for separating chromosomes during mitosis.[14] Microtubules are normally highly dynamic, oscillating between assembly and disassembly.[15] By binding to beta-tubulin, taxanes disrupt microtubule dynamics, blocking cell cycle progression through mitosis and eventually inducing apoptosis in rapidly dividing cells.[10,16,17] This is believed to be the main mechanism for taxanes to inhibit the growth of cancer cells. However, in prostate cancer cells, taxanes have been reported to directly impact the androgen receptor (AR) signaling pathway, and inhibiting AR signaling, instead of inducing mitotic arrest, has been indicated to mediate the therapeutic efficacies of taxanes in prostate cancer.[18] In this

review, we will summarize the preclinical and clinical data on the potential impact of taxanes on AR signaling.

EFFECTS OF DOCETAXEL AND PACLITAXEL ON AR SIGNALING

Full-length AR

Androgen-induced translocation of the full-length AR (AR-FL) to the nucleus, which is required for the transcriptional activity of AR-FL, has been reported to use a microtubule-facilitated pathway.[19–22] Consequently, as reported by several groups, by stabilizing microtubules, docetaxel and paclitaxel might attenuate AR-FL nuclear import. The first report was from Zhu *et al.*[22] in 2010, showing that, in prostatectomy tissues from 50 patients enrolled in a neoadjuvant chemotherapy study, docetaxel treatment led to a decrease in the percentage of tumor cells exhibiting nuclear accumulation of AR (38% in the docetaxel group *vs* 50% in the control group), which correlated with the expression of the classical AR target gene, prostate-specific antigen (*PSA*). Consistently, pretreatment of AR-expressing LNCaP prostate cancer cells with 1 μmol l⁻¹ paclitaxel for 24 h almost abrogated androgen-induced AR-FL nuclear translocation, PSA expression, and AR transcriptional activity.[22] The authors further demonstrated the physical interaction between AR and tubulin in a co-immunoprecipitation assay.[22]

The above findings were subsequently substantiated by several other groups. In 2011, Darshan *et al.*[21] reported a similar impairment of AR nuclear accumulation in LNCaP cells pretreated with 100 nmol l⁻¹ paclitaxel overnight and in PC-3 cells microinjected with green fluorescent protein-tagged AR (GFP-AR) and treated with 1 μmol l⁻¹ paclitaxel for up to 2 h. They further showed that AR prefers to bind to the microtubule polymers than to bind to the tubulin dimers and that the effect of paclitaxel on AR nuclear translocation was dependent on its ability to stabilize microtubules.[21] Importantly, analysis of circulating tumor cells isolated from 14 mCRPC patients receiving paclitaxel or docetaxel therapy revealed a significant

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correlation between AR cytoplasmic retention and clinical response.[21] Likewise, van Soest *et al.*[23] found that pretreatment of PC346C prostate cancer cells stably expressing GFP-AR with 1 μmol l⁻¹ docetaxel for 4 h inhibited androgen induction of AR-FL nuclear localization. In a later study, they confirmed this observation *in vivo* and showed that treatment of castrated mice bearing PC346C tumors with a single intraperitoneal injection of 33 mg kg⁻¹ docetaxel reduced the nuclear staining of the endogenous AR by 75%.[24]

While the above preclinical and clinical evidences support a role of paclitaxel and docetaxel in inhibiting AR-FL nuclear localization and transcriptional activity, it remains controversial as to whether this is a direct effect that is relevant to clinically attainable doses of paclitaxel and docetaxel. Although pharmacokinetic studies showed that plasma levels of docetaxel in patients receiving near the maximum-tolerated dose of docetaxel could reach μmol l⁻¹ concentrations,[25–27] whether this is achievable in the tumors is unclear. Since the *in vitro* IC$_{50}$ doses of this class of drugs are in the single nanomolar range, de Leeuw *et al.*[28] tested the effect of 1 nmol l⁻¹ docetaxel on AR-FL nuclear localization in LNCaP and C4-2 prostate cancer cells after 16 h of treatment but did not detect any inhibition. They further treated *ex vivo* culture of fresh tissues obtained from radical prostatectomy with 50 nmol l⁻¹ of docetaxel for 6 days, and no change in AR-FL subcellular localization was observed.[28] While these findings argue against a direct effect of docetaxel on AR-FL nuclear translocation, Zhang *et al.*[19] showed that treating COS7 cells with 10 nmol l⁻¹ of docetaxel for 24 h following androgen stimulation or pretreating COS7 cells with 10 nmol l⁻¹ docetaxel for 6 h followed by androgen stimulation inhibited the nuclear accumulation of the transfected GFP-AR-FL. Using the fluorescence recovery after photobleaching assay, the authors further demonstrated that this was due to deterred nuclear import.[19] However, the same study also showed that docetaxel at a lower concentration, 1 nmol l⁻¹, was sufficient to inhibit androgen induction of AR-FL transactivation.[19] Interestingly, Darshan *et al.*[21] also showed an inhibition of AR-FL transactivation by docetaxel at a dose that was two orders of magnitude lower than the dose reported for blocking AR-FL nuclear localization (10 nmol l⁻¹ *vs* 1 μmol l⁻¹).[20] This raised the possibility of a nuclear-localization-independent mechanism of AR signaling inhibition. In fact, an early report by Gan *et al.*[29] showed that treatment of 22Rv1 cells with 1 nmol l⁻¹ of paclitaxel for 24 h induced the expression and nuclear localization of forkhead box protein O1 (FOXO1), an AR co-repressor, as well as the association of FOXO1 and AR-FL proteins in the nucleus and the binding of FOXO1 to the *PSA* promoter. They further demonstrated that knockdown of FOXO1 attenuated paclitaxel inhibition of AR transcriptional activity and induction of apoptosis, indicating a direct involvement of an AR co-repressor in paclitaxel inhibition of AR signaling and cell growth.[29]

In summary, the AR-FL protein could be sequestered in the cytoplasm by high-dose docetaxel or paclitaxel, while more studies are needed to demonstrate how much this mechanism contributes to their clinical efficacies. Nonetheless, it is likely that docetaxel and paclitaxel could inhibit AR signaling through an additional mechanism(s).

AR splice variants (AR-Vs)

AR-Vs are generated by alternative splicing of the AR pre-mRNA, in some cases, due to structural rearrangements of the *AR* gene.[30–37] To date, over 20 AR-Vs have been identified in human prostate cancer cell models and clinical specimens.[38] Some AR-Vs, such as AR-V7 and AR^{v567es}, are constitutively active and have been implicated in castration resistant progression of prostate cancer.[38] However, whether AR-Vs play a role in modulating taxane response is still unclear. Clinically,

pretherapy detection of AR-V7 mRNA or protein in circulating tumor cells from mCRPC patients was shown not to be associated with primary resistance to docetaxel chemotherapy.[39,40] While additional prospective biomarker-stratified clinical trials are needed to validate these findings, the available clinical evidence indicates that the contribution of AR-V7 to docetaxel resistance is not as significant as that to AR-directed therapies[39–41] and that docetaxel therapy may be more effective than AR-directed therapies for patients with AR-V7-positive mCRPC. This appears to be in contrast to preclinical findings. Two preclinical studies assessed the roles of AR-V7 and AR^{v567es} in mediating taxane resistance. Although it remains controversial as to whether AR^{v567es} is sensitive to docetaxel modulation, there appears to be a consensus from both studies on the resistance of AR-V7 to docetaxel inhibition of nuclear localization.[19,20] AR-V7 and AR^{v567es} both retain an intact N-terminal domain and DNA-binding domain but lack the ligand-binding domain (**Figure 1**). The major structural difference between these two AR-Vs is that AR^{v567es} contains, but AR-V7 lacks, the hinge region (**Figure 1**), which includes a motif that is important for AR nuclear localization,[42] activity, and mobility inside the nucleus[43] and is also a target for acetylation[44,45] and methylation.[46] Using the microtubule co-sedimentation assay, Thadani-Mulero *et al.*[20] mapped the microtubule-binding domain of AR to the DNA-binding domain plus the hinge region and showed that AR^{v567es}, but not AR-V7, co-sedimented with microtubules. Concordantly, pretreatment of PC-3 or M12 prostate cancer cells with 1 μmol l⁻¹ docetaxel for 2 h or 4 h, respectively, inhibited the nuclear localization and transcriptional activity of ectopically-expressed AR^{v567es}, but not AR-V7.[20] In addition, the authors showed that docetaxel treatment led to a significant reduction of nuclear AR^{v567es} staining in LuCaP86.2 human prostate cancer xenografts and inhibited the growth of the xenografts,[20] and there is an initiative from the Prostate Cancer Foundation, the Movember Foundation, and Science Exchange to replicate this experiment.[47] On the other hand, using the *in vivo* microtubule binding assay, Zhang *et al.*[19] demonstrated that the ligand-binding domain of AR was sufficient to associate with microtubules and that neither AR-V7 nor AR^{v567es} bound to microtubules. Consistently, treating COS7 cells with 20 nmol l⁻¹ of docetaxel for 2 h did not affect the nuclear entry of GFP-AR-V7 or red-fluorescent-protein-tagged AR^{v567es} while significantly deterred androgen-induced nuclear entry of GFP-AR-FL.[19] Moreover, ectopic expression of AR-V7 or AR^{v567es} in LNCaP cells attenuated docetaxel growth inhibition, and conversely, knockdown of AR-V7 enhanced docetaxel growth inhibition in LNCaP95 cells, castration-resistant derivative of LNCaP.[19] The disparity between these two studies on AR^{v567es} might be due to the use of different microtubule-binding assays and different doses of docetaxel; nonetheless, both studies provided preclinical support for a role of AR-V7 in mediating docetaxel resistance.

Interestingly, Zhang *et al.*,[19] also showed that co-transfection of AR-V7 or AR^{v567es} with AR-FL greatly attenuated the binding of
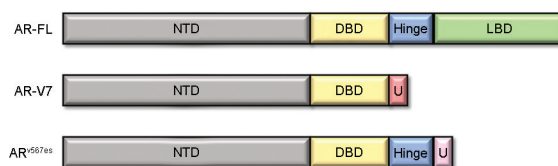
Figure 1: Schematic representation of the structure of AR-FL, AR-V7, and AR^{v567es} proteins. NTD: N-terminal domain; DBD: DNA-binding domain; LBD: ligand-binding domain; U: peptide unique to AR-V7 or AR^{v567es}; AR-V7: androgen receptor splice variant 7; AR-FL: full-length androgen receptor. Drawings are not to scale.

AR-FL to the microtubules and docetaxel sequestration of AR-FL in the cytoplasm. Endogenous co-expression of AR-Vs with AR-FL in 22Rv1 cells and xenografts has also been shown to negate the inhibitory effects of docetaxel on AR-FL nuclear localization and transcriptional activity.[48] We previously showed that AR-V7 and AR[v567es] can induce androgen-independent AR-FL nuclear translocation and transactivation.[49,50] The attenuated effect of docetaxel on AR-FL nuclear translocation in the presence of AR-V7 or AR[v567es] might be due to a microtubule-independent pathway of AR-FL nuclear transport that is facilitated by AR-V7/AR[v567es]. Taken together, the above preclinical findings point to a role of constitutively active AR-Vs in mediating docetaxel resistance, which could be through both their intrinsic resistance to docetaxel modulation and their mitigation of docetaxel inhibition of AR-FL. More studies are needed to determine the clinical relevance of the findings and to reconcile the discrepancy between preclinical and clinical observations.

EFFECT OF CABAZITAXEL ON AR SIGNALING

Albeit also a taxane drug and disrupting microtubule dynamics by binding to beta-tubulin,[7] cabazitaxel has been shown by several groups not to impact AR nuclear translocation. Clinically, the therapeutic response of mCRPC patients to cabazitaxel was shown to be independent of the presence of AR-V7 in circulating tumor cells.[39,40,51] Preclinically, while the initial study by van Soest *et al*.[23] showed that pretreatment of PC346C cells stably expressing GFP-AR with 1 μmol l^{−1} cabazitaxel for 4 h inhibited androgen induction of AR-FL nuclear localization, they were not able to recapitulate the observation *in vivo* in PC346C xenograft tumors with the endogenous AR.[24] The lack of effect was also reported by de Leeuw *et al*.[28] in LNCaP and C4-2 cells and in *ex vivo* culture of prostatectomy tissues when the cells or the *ex vivo* culture were treated with 1 nmol l^{−1} cabazitaxel (an *in vitro* IC$_{50}$ dose) for 16 h or 50 nmol l^{−1} cabazitaxel for 6 days, respectively. Similarly, Martin *et al*.,[52] found no change in AR nuclear localization by cabazitaxel in LNCaP cells after 24 h or 48 h of treatment with 25 nmol l^{−1} cabazitaxel, in dominant-negative-transforming growth factor (TGF)-βRII-expressing transgenic adenocarcinoma of mouse prostate (TRAMP) mice, or in 22Rv1 xenograft tumors.[45] Al Nakouzi *et al*.[53] further showed that cabazitaxel, at 2.5 nmol l^{−1} or 10 nmol l^{−1} concentration, did not directly impact androgen induction of AR-FL nuclear localization or transcriptional activity in three castration-resistant LNCaP xenograft-derived cell lines, CRPC-V16D, MR49C, and MR49F. Importantly, they demonstrated that the growth inhibitory efficacy of cabazitaxel in these cells was not affected by AR knockdown, providing direct evidence to support the AR-independent mechanisms of action of cabazitaxel.[53] Taken together, these clinical and preclinical findings suggest that cabazitaxel functions mainly via AR-independent mechanisms in prostate cancer.

CONCLUSION

Docetaxel and cabazitaxel appear to have different mechanisms of action in prostate cancer, although both being microtubule-stabilizing taxane. Docetaxel can inhibit AR signaling through repressing AR-FL transcriptional activity and/or nuclear localization, while cabazitaxel functions mainly via AR-independent mechanisms. Patients with progressive mCRPC after treatment with abiraterone, a second-generation androgen deprivation therapy, have been shown to have impaired response to subsequent docetaxel-based chemotherapy than abiraterone-naïve patients.[54,55] However, this issue of cross-resistance does not seem to exist between abiraterone and cabazitaxel. Cabazitaxel was showed to retain clinical activity in

patients refractory to abiraterone.[53] The divergence in the involvement of AR signaling in the actions of docetaxel and cabazitaxel may constitute a mechanism underlying the presence or absence of cross-resistance between different taxanes and AR-targeted agents. Moreover, the recently published CHAARTED and STAMPEDE trials showed that combining docetaxel with androgen deprivation therapy in men with hormone-naïve metastatic prostate cancer produced a robust overall survival benefit of 13.6–15 months compared to androgen deprivation therapy alone,[56,57] a benefit much greater than when docetaxel is used in the castration-resistant setting. Several mechanisms have been proposed to underlie the improved efficacy, for example, early killing of the castration-resistant clones[56] or increased clearance of docetaxel in castrated compared to gonad-intact men.[58] Could the improved efficacy be also attributed by the ability of docetaxel to inhibit androgen-induced AR transactivation in the hormone-naïve setting? If so, on the basis of its AR-independent mechanism of actions, would cabazitaxel yield less benefit in the hormone-naïve setting than the castration-resistant setting compared to docetaxel? The ongoing SensiCab randomized phase III trial (ClinicalTrials.gov identifier: NCT01978873), which is to compare cabazitaxel in combination with androgen deprivation therapy to androgen deprivation therapy alone in metastatic prostate cancer, the Phase II Multicenter Trial of Abiraterone Acetate With or Without Cabazitaxel in Treatment of mCRPC (ClinicalTrials.gov identifier: NCT02218606), and the Phase I/II Trial of Concurrent Chemohormonal Therapy Using Enzalutamide (MDV-3100) and Cabazitaxel in Patients With mCRPC (ClinicalTrials.gov identifier: NCT02522715) would help address these questions to enable a tailored therapeutic strategy in selecting patients who may benefit the most from specific treatment at specific point of disease progression.

AUTHOR CONTRIBUTIONS

SB, BYZ, and YD contributed to the conception, literature search, literature reading and analysis, as well as writing and revision of the manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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