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Prostate Cancer

Taxane Mechanisms of Action: Potential Implications for Treatment Sequencing in Metastatic Castration-resistant Prostate Cancer

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Abstract

Context: In the past few years, there has been a rapid increase in the number of therapies available to treat metastatic castration-resistant prostate cancer (mCRPC). Currently, approved treatments consist of the taxane class of cytotoxic drugs and androgen-targeted therapies. The challenge for clinicians is to decide the best sequence in which to give these therapies to provide the greatest benefit to their patients.
Objective: To review recent research into the mechanism of action of taxanes in prostate cancer (PCa) cells and the clinical evidence for an interaction between taxanes and androgen-targeted therapies. The implications of these findings for clinical practice are discussed.
Evidence acquisition: A nonsystematic review of the relevant medical literature between 2004 and the present, in combination with clinical trial data reported at oncology meetings during 2012, was undertaken. Our perspective, focussing on the potential implications for sequencing of therapies for mCRPC, is provided.
Evidence synthesis: Taxanes are shown to interact with androgen signalling in PCa cells at both the cytoplasmic level (via microtubules) and the nuclear level, affecting transcriptional regulators of androgen-responsive gene expression. Data from clinical trials suggest that androgen deprivation can potentially decrease the efficacy of taxanes in treating PCa.
Conclusions: These findings have important implications for clinical practice, and there is an urgent need for strong clinical data to support a recommendation for an optimal sequence of therapies.

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1. Introduction

Prostate cancer (PCa) is a major cause of cancer mortality in Europe and the United States. In recent years, the taxane class of cytotoxic chemotherapeutic agents has been shown to provide a survival benefit in advanced PCa, inhibiting tumour development and decreasing prostate-specific antigen (PSA) levels [1–3]. Taxanes act by stabilising microtubules, the intracellular filaments that are part of the cell's cytoskeleton. Microtubules are involved in cell shape, vesicle transport, transcription factor trafficking, mitochondrial functioning, and cell signalling, as well as their best-known role in chromosome separation during cell division and mitosis. The binding of taxane molecules to

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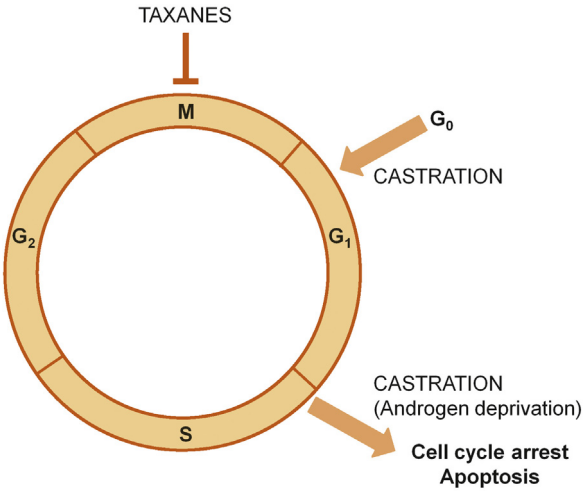

Fig. 1 – Cell cycle diagram indicating the checkpoints at which taxanes and androgen deprivation block progression, leading to cell cycle arrest and apoptosis.

microtubules prevents their disassembly, which leads to cell cycle arrest in metaphase–anaphase, as indicated in Figure 1 [4]. With cell cycle progression blocked, cells eventually die by apoptosis [5]. Taxanes most likely promote apoptosis by inhibiting the antiapoptotic function of the B-cell CLL/lymphoma 2 (BCL2) family [5,6] and upregulating cyclin-dependent kinase inhibitor 1A (p21, Cip1) and tumour protein p53, which arrest the cell cycle. Recently, however, it has been proposed that the clinical efficacy of taxanes may actually be due to their inhibition of essential interphase cellular mechanisms involving microtubules rather than their effect on mitosis [7].

Although taxanes inhibit tumour growth and improve survival in advanced PCa and other settings such as breast, ovarian, and lung cancer, development of resistance is inevitable, and patients' disease will eventually progress. Resistance can develop through a variety of mechanisms. Increased transport of the drug out of tumour cells by upregulation of ATP-binding cassette transporter molecules in the cell membrane, such as P-glycoprotein, is a common resistance mechanism. The taxane cabazitaxel was selected to address taxane resistance on the basis of its activity in taxane-resistant P-glycoprotein-expressing colon, breast, and gastric tumour cell lines. Tubulin mutations that affect the binding site for taxanes are an important mechanism of resistance, and distinct differences in binding modes may account for the lack of cross-resistance between different taxanes (e.g. docetaxel, paclitaxel and cabazitaxel) and other microtubule-stabilising drugs [8].

Mechanisms of docetaxel resistance also include inhibition of apoptosis [9,10] and activation of the extracellular signal-related kinase/mitogen-activated protein kinase or phosphatidylinositol-3 kinase/Akt survival pathways [11,12]. Most recently, docetaxel-resistant PCa cells have been demonstrated to exhibit an epithelial–mesenchymal transition (EMT) phenotype [13], linking docetaxel resistance with the development of metastasis, and upregulation of the zinc finger E-box binding homeobox 1 (ZEB1) transcription factor, a direct regulator of EMT, can confer docetaxel resistance [14]. An understanding of how these mechanisms contributing to taxane resistance may interact will be important when considering the sequence of therapies for advanced PCa.

In the initial stages of advanced disease, PCa is dependent on androgen signalling for development and can be suppressed by androgen-deprivation therapy (ADT), which blocks mitogen-dependent G1–S-phase progression through the cell cycle, as shown in Figure 1 [15]. However, at some stage the disease will progress despite low levels of testosterone. Two theories explain tumour regrowth with ADT. The first theory involves the "adaptation" of androgen-sensitive cells to low circulating levels of testosterone via various mechanisms, including androgen receptor (AR) amplification, AR gain-of-function mutations, ligand-independent activation of AR, deregulation of the AR/coregulator/corepressor control, and de novo androgen synthesis by tumour cells. In the second theory, tumour regrowth is due to the clonal proliferation of AR-insensitive cells during ADT [16].

PCa is a heterogeneous disease, and both theoretical mechanisms of tumour regrowth are likely to coexist in the vast majority of patients. Although it would be difficult to identify which is the predominant pathway of progression in a given individual, doing so could help guide treatment decisions.

It is important to note that the androgen-signalling pathway is active during PCa progression, with androgens being produced by the adrenal glands and the tumour microenvironment, in addition to the testes. This activity is the rationale for androgen-directed therapies such as abiraterone and enzalutamide, which have shown survival benefits in castration-resistant PCa (CRPC) [17,18]. Conversely, the emergence of aggressive castration-resistant clones during ADT is the rationale for taxane-based therapy, which is the only chemotherapy class to show a survival benefit in metastatic CRPC (mCRPC) [1–3].

In addition to promoting cell growth, androgens can influence EMT of PCa cells, potentially contributing to their metastatic behaviour. Androgen signalling in PCa cells has been shown to induce changes characteristic of EMT and cytoskeletal reorganisation, which are part of the metastatic behaviour of CRPC cells [19]. However, several other studies have linked androgen ablation with EMT markers in PCa cell lines and human clinical samples [20]. The EMT phenotype was also associated with increased stem cell characteristics and activated transforming growth factor β (TGF-β) signalling, which may perhaps underlie the induction of EMT by androgen signalling reported by Zhu et al. in TGF-β-responsive lymph node carcinoma of the prostate cell lines [19,20]. In particular, androgen ablation was demonstrated to increase levels of the transcription factor *ZEB1* in a variety of models, and conversely, *AR* expression could be repressed by ZEB1 [20]. This negative feedback loop between the AR and ZEB1 implies that androgen ablation, though effective in controlling prostate tumour size, could ultimately lead to tumour metastasis and castration resistance via promotion