

# The role of cabazitaxel in the treatment of metastatic castration-resistant prostate cancer

Che-Kai Tsao, Elena Cutting, Jacob Martin and William K. Oh

**Abstract:** For decades, cytotoxic therapy was considered ineffective for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Earlier therapies such as estramustine and mitoxantrone received regulatory approval based upon improvement in palliative endpoints. In 2004, docetaxel became the first treatment to demonstrate a significant survival benefit in patients with mCRPC based on two randomized phase III studies, TAX327 and SWOG 99-16. Cabazitaxel, a third-generation taxane, was chosen for clinical development based on its decreased affinity for the drug efflux pump, p-glycoprotein, which is a frequent cause of drug resistance in docetaxel-resistant preclinical models. In 2010, cabazitaxel was approved by the US Food and Drug Administration as the first therapy to show a survival benefit for the treatment of patients with docetaxel-refractory mCRPC. This review summarizes the existing literature on the use of cabazitaxel, focusing on its efficacy and safety in combination with prednisone in the treatment of mCRPC, as well as its role in an era of new therapeutic options.

**Keywords:** cabazitaxel, castration resistant, docetaxel, efficacy, prostate cancer, safety, taxane

## Introduction

Despite advances in screening and treatment, prostate cancer remains a leading cause of cancer death among men, with an expected 29,720 deaths in 2013 [Siegel *et al.* 2013]. While the use of prostate-specific antigen (PSA) screening increased early disease detection and therapy, a subset of patients inevitably develop metastatic disease, which is considered incurable. Androgen-deprivation therapy via surgical orchiectomy or gonadotropin-releasing hormone agonists or antagonists leads to castrate levels of testosterone and is temporarily effective in most patients with advanced prostate cancer. However, eventual progression results in a lethal disease phenotype known as metastatic castration-resistant prostate cancer (mCRPC) [Tsao *et al.* 2012]. mCRPC was historically thought to be chemotherapy resistant [Scher and Sawyers, 2005], but recent studies have demonstrated that this is not the case.

Taxanes bind microtubules, promoting their stabilization and preventing cellular mitosis and division [Jordan and Wilson, 2004] (Figure 1). Additionally, taxanes inhibit androgen receptor (AR) signaling by binding cellular microtubules and the microtubule-associated motor protein dynein, and consequently preventing AR nuclear translocation [Darshan *et al.* 2011] (Figure 1). Paclitaxel was the first taxane to receive regulatory approval in the United States as an anticancer therapy. Docetaxel, a second-generation semisynthetic taxane analog with better tolerability and cytotoxicity, was initially approved by the US Food and Drug Administration in 1996 for the treatment of advanced breast cancer. Promising early phase trials led to two phase III studies evaluating its role in the treatment of mCRPC [Picus and Schultz, 1999]. In the TAX 327 study, 1006 patients were randomized to receive prednisone and either docetaxel (30 mg/m<sup>2</sup> weekly or 75 mg/m<sup>2</sup> every 3 weeks) or

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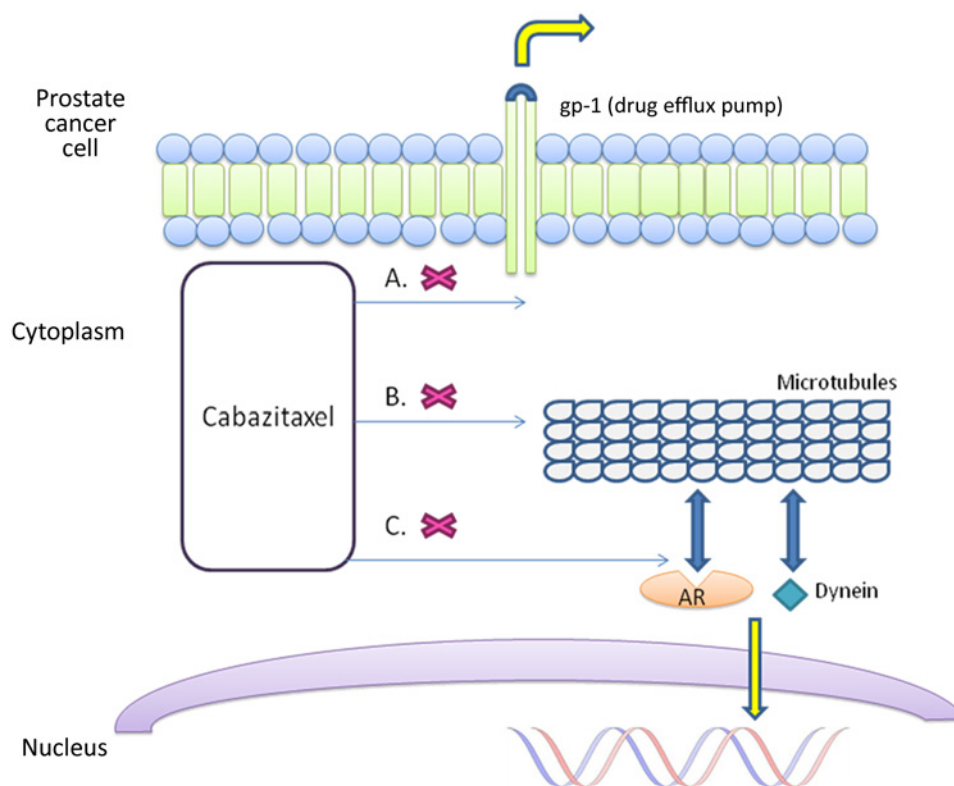
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**Figure 1.** Cabazitaxel: mechanism of action.

A. Lower affinity for the drug efflux pump p-glycoprotein 1 [gp-1]. B. Bind cellular microtubules to promote stabilization and prevent cellular mitosis and division. C. Bind cellular microtubules and the microtubule-associated motor protein dynein to inhibit androgen receptor nuclear translocation.

mitoxantrone 12 mg/m<sup>2</sup> every 3 weeks. Treatment with docetaxel every 3 weeks was associated with a significant improvement in overall survival compared with mitoxantrone, and additionally led to improvement in other secondary endpoints such as pain and quality of life [Tannock *et al.* 2004]. In the SWOG 99-16 trial, patients with mCRPC were randomized to receive estramustine and docetaxel *versus* mitoxantrone and prednisone, and again docetaxel was associated with a significant benefit in overall survival [Petrylak *et al.* 2004]. However, due to concerns that estramustine/docetaxel coadministration is comparably associated with more significant myelosuppression and gastrointestinal toxicities, docetaxel plus prednisone has become the standard of care for the first-line treatment of progressive mCRPC in the past decade.

In the past several years, there has been a surge of drug approvals for mCRPC, including sipuleucel-T, abiraterone acetate, enzalutamide and radium-223. While these new drugs represent true progress, each treatment has limited activity

and unfortunately none of these therapies is curative. Thus effective treatment options after progression on docetaxel remains a significant clinical challenge.

#### Cabazitaxel: preclinical data

Preclinical studies of taxane-resistant tumors revealed a high substrate affinity for the adenosine triphosphate dependent drug efflux pump, p-glycoprotein 1 (gp-1). Specifically, upregulation of drug excretion is responsible, at least in part, for inherent and acquired resistance to these agents [Mita *et al.* 2009]. This observation led to the clinical development of cabazitaxel (Jevtana; Sanofi-Aventis, New Jersey, USA) (XRP6258, RPR 116258A and TXD258), a compound selected specifically for its poor affinity to gp-1.

Cabazitaxel (formula C<sub>45</sub>H<sub>57</sub>NO<sub>14</sub>) is a dimethoxy derivative of docetaxel and is partially synthesized into a single diastereomer from 10-deacetyl baccatin III, the major natural taxane found in the needles of various *Taxus* species

[Mita *et al.* 2012]. In prostate cancer cell lines including DU145, a known castration-resistant prostate cancer cell line, as well as mouse models of prostate cancer, cabazitaxel demonstrated significant antitumor activity. Importantly, cabazitaxel retains significant cytotoxicity in docetaxel-resistant cell lines due to gp-1 overexpression. Another attractive property of cabazitaxel is its enhanced solubility in water-based solutions compared with other taxanes, enabling better blood–brain barrier penetration resulting in higher central nervous system drug concentrations with systemic administration in mouse models.

### Early clinical studies

Two phase I studies evaluated the safety and pharmacokinetic properties of cabazitaxel across various solid tumor types. In the first study between 1999 and 2001, 25 patients (eight with mCRPC) were treated with 102 courses of cabazitaxel, from 10 to 25 mg/m<sup>2</sup> intravenously every 3 weeks [Mita *et al.* 2012]. Although the treatment was generally well tolerated up to 25 mg/m<sup>2</sup>, grade 4 neutropenia was commonly observed at this dose, and the investigators concluded that a dose of 20 mg/m<sup>2</sup> every 3 weeks is appropriate for further clinical testing. Further, of three patients who achieved partial responses to treatment, two had mCRPC, including one who had previously been treated with docetaxel. Another phase I study concluded that the limiting hematologic dose-limiting toxicity was seen at 30 mg/m<sup>2</sup> [Diéras *et al.* 2012]. Two separate phase II studies in women with metastatic breast cancer were reported, further establishing the efficacy and safety of cabazitaxel despite prior disease progression on taxane therapy [Pivot *et al.* 2008; Villaneuva *et al.* 2011].

### Phase III data: TROPIC study

A strategic decision was made to proceed directly to a randomized, multicenter phase III study known as TROPIC, without first conducting phase II studies in men with mCRPC. In the TROPIC study, 755 men with mCRPC who previously received docetaxel chemotherapy were randomized to receive either cabazitaxel 25 mg/m<sup>2</sup> ( $n = 378$ ) or mitoxantrone 12 mg/m<sup>2</sup> ( $n = 377$ ) every 3 weeks for a maximum of 10 cycles, concurrently with prednisone 10 mg daily [de Bono *et al.* 2010]. To ensure docetaxel resistance, an interim protocol amendment mandated that study subjects

must have received a cumulative dose of docetaxel greater than 225 mg/m<sup>2</sup>, with only 8% ( $n = 59$ ) of study subjects failing to meet this requirement. Additionally, half of the patients enrolled had at least one site of soft tissue metastasis, with 25% having visceral disease, indicating that patients in the study generally had advanced mCRPC.

At the first interim analysis, with a median follow up of 12.7 months, median overall survival was 15.1 months for the cabazitaxel group *versus* 12.7 months for the mitoxantrone group, corresponding to a 30% reduction in relative risk of death (hazard ratio 0.70, 95% confidence interval 0.59–0.83,  $p < 0.0001$ ). Other clinical endpoints, including PSA response and progression, objective tumor progression and pain progression all favored the cabazitaxel treatment arm (Table 1). A recent updated analysis 2 years after the original TROPIC data cutoff (March 2012) confirmed a sustained survival benefit with longer follow up, with cabazitaxel treatment being predictive of survival over 2 years [Bahl *et al.* 2012].

## Pharmacology

### Pharmacokinetics

In phase I studies, the decline in plasma concentrations after cabazitaxel administration demonstrated triphasic kinetics: first phase with a mean half life ( $t_{1/2}$ ) of 2.6 min; second phase with a mean  $t_{1/2}$  of 1.3 h; and a prolonged third phase with a mean  $t_{1/2}$  of 77.3 h. Cabazitaxel is equally distributed between blood and plasma [Mita *et al.* 2009].

### Metabolism and drug interaction

Cabazitaxel is mainly metabolized by the liver [cytochrome P450 (CYP)3A4/5 > CYP2C8], with seven plasma metabolites, and additionally 20 metabolites when excreted. Approximately 80% of cabazitaxel is excreted within 14 days of administration, primarily in the feces (76%). Renal excretion is responsible for 3.7% (2.3% as unchanged drug).

Cabazitaxel is primarily metabolized by CYP3A *in vivo* and its pharmacokinetics is expected to be affected by both inducers and inhibitors of CYP3A.

### Safety profile

Consistently observed throughout clinical testing of cabazitaxel is a high frequency of hematologic toxicity (Table 2). In the TROPIC study, a total of

**Table 1.** Clinical efficacy of therapies approved for docetaxel-resistant prostate cancer.

Treatment	Overall survival (months)	Response rate (%)	Time to PSA progression (months)	Radiographic progression-free survival (months)	Palliative endpoints
Cabazitaxel + prednisone versus mitoxantrone + prednisone (TROPIC)	15.1 versus 12.7	14.4 versus 4.4	6.4 versus 3.1	8.8 versus 5.4	Similar pain response rate (9.2% versus 7.7%) Two-year follow-up study shows an improvement in daily pain performance index
Abiraterone + prednisone versus prednisone (COU-AA-301)	15.8 versus 11.2	14 versus 3	8.5 versus 6.6	5.6 versus 3.6	Improvement in pain score (44% versus 27%) Improvement in time to 25% having a skeletal event (9.9 versus 4.9 months)
Enzalutamide versus placebo (AFFIRM)	18.4 versus 13.6	29 versus 4	8.3 versus 3.0	8.3 versus 2.9	Improvement in FACT-P quality-of-life response (43% versus 18%, $p < 0.001$ ) Improvement in time to first skeletal-related event (16.7 versus 13.3 months)

371 patients received 25 mg/m<sup>2</sup> of cabazitaxel every 3 weeks, and neutropenia (94%), anemia (97%) and thrombocytopenia (47%) were commonly seen. Specifically, 82% of the patients experienced grade 3–4 neutropenia, 8% experienced neutropenic fever, and five patients experienced fatal adverse infectious events. Grade 3–4 anemia (11%) and thrombocytopenia (4%) were far less common (Table 1).

Common nonhematologic toxicities were mainly gastrointestinal in nature: diarrhea (47%), nausea (34%), vomiting (22%) and constipation (20%). Importantly, in this population of patients who previously received docetaxel, significant peripheral neuropathy (grade 3–4) was observed in less than 1% of patients. Commonly reported adverse effects were fatigue (37%), asthenia (20%) and hematuria (17%), with the most commonly reported nonhematologic grade 3–4 adverse events being diarrhea (6%), fatigue (5%) and

asthenia (5%). Postmarketing surveillance has led to identification of other previously unreported adverse effects, mainly gastrointestinal and infectious in nature, although given that the sample size is unknown the frequency cannot be accurately quantified.

Whether the safety profile of a drug reported in a phase III clinical trial can translate to ‘real world’ patients has been evaluated in several expanded access programs. A German compassionate use program with 111 patients reported a comparable treatment efficacy, but with far fewer ‘treatment-emergent adverse events’ [Heidenreich *et al.* 2013]. A larger study in older patients also reported a manageable safety profile in practice [Heidenreich *et al.* 2014]. Factors such as age at least 75 years, treatment cycle 1 and neutrophil count less than 4000/mm<sup>3</sup> before cabazitaxel injection were associated with increased risk of developing grade 3 or higher neutropenia and

**Table 2.** Common adverse effects of cabazitaxel.

Adverse event	All events	Grade $\geq 3$	Special considerations
<i>Hematologic</i>			
Neutropenia	347 (94%)	303 (82%)	More common age $\geq 65$ ; consider G-CSF prophylaxis
Leukopenia	355 (96%)	253 (68%)	
Anemia	361 (97%)	39 (11%)	
Thrombocytopenia	176 (47%)	15 (4%)	
<i>Nonhematologic</i>			
Diarrhea	173 (47%)	23 (6%)	More common age $\geq 75$ and prior radiotherapy
Fatigue	136 (37%)	18 (5%)	
Back pain	60 (16%)	14 (4%)	
Nausea	127 (34%)	7 (2%)	
Vomiting	84 (23%)	7 (2%)	
Hematuria	62 (17%)	7 (2%)	
Abdominal pain	43 (12%)	7 (2%)	
Dyspnea	44 (12%)	5 (1%)	
Constipation	76 (20%)	4 (1%)	
Pyrexia	45 (12%)	4 (1%)	
Arthralgia	39 (11%)	4 (1%)	
<i>Postmarket reporting (frequency not determined)</i>			
Colitis, enterocolitis, gastritis, neutropenic enterocolitis, gastrointestinal hemorrhage and perforation, ileus and intestinal obstruction			
G-CSF, granulocyte colony stimulating factor.			

neutropenic complications. In fact, prophylactic use of granulocyte colony-stimulating factor (G-CSF) significantly reduced this risk by 30% in each cycle of therapy (odds ratio 0.70,  $p = 0.04$ ). These results have led to the hypothesis that aggressive counseling and prophylactic G-CSF use may be effective in reducing adverse events.

## Special patient populations

### *Geriatric use*

Although population pharmacokinetic analysis did not demonstrate significant differences in geriatric patients (age  $> 65$ ), these older patients were more likely to experience adverse reactions, including neutropenia, fatigue, asthenia, pyrexia, dizziness, urinary tract infection and dehydration. Close monitoring, routine use of prophylactic G-CSF, and aggressive and early therapy for signs of infection should be strongly considered in this population.

### *Organ impairment*

Despite lack of clinical trial enrollment of patients with liver function impairment, cabazitaxel is

metabolized mainly by the liver and is not recommended for use if total bilirubin or transaminases are above 1.5 times the upper normal limit. Conversely, although there are no specific guidelines, therapy in patients with renal impairment could be considered with close monitoring.

## Optimal timing and dose of cabazitaxel

Even after the regulatory approval of cabazitaxel in the treatment of docetaxel-refractory mCRPC, many questions remain with regard to its optimal use, leading to further clinical testing to answer these important questions (Table 3). One question is the optimal dose and frequency of cabazitaxel administration in men with mCRPC. Given concerns of significant myelosuppression with administration of cabazitaxel at 25 mg/m<sup>2</sup>, an ongoing randomized phase III study will evaluate the safety and efficacy of cabazitaxel at 20 mg/m<sup>2</sup>. In addition, alternative schedules of cabazitaxel administration are being evaluated. The role of supportive care measures such as prophylactic G-CSF and antibiotics to minimize complications associated with myelosuppression are also the subject of ongoing studies. In fact, many

**Table 3.** Ongoing clinical trials of cabazitaxel.

ClinicalTrials.gov identifier	Trial summary	Study phase/enrollment	Primary endpoint	Target completion date
<i>Dose and frequency</i>				
NCT01518283	4 weekly cabazitaxel 10 mg/m <sup>2</sup> of 5-week cycle	II (n = 74)	PSA progression	September 2014
NCT01558219	Cabazitaxel 16 mg/m <sup>2</sup> every 2 weeks	II (n = 60)	Safety and tolerability	December 2014
NCT01541007	5 weekly cabazitaxel 10 mg/m <sup>2</sup> of 6-week cycle	II (n = 100)	Cumulative dose	June 2015
NCT01308580	Compare 20 mg/m <sup>2</sup> with 25 mg/m <sup>2</sup>	III (n = 1200)	Overall survival	September 2017
<i>Combination therapy (with cabazitaxel)</i>				
NCT01845792	Abiraterone/prednisone	I/II (n = 72)	PSA reduction	July 2019
NCT01505868	Carboplatin	I/II (n = 178)	Progression-free survival	July 2029
NCT01578655	Custirsen	III (n = 630)	Overall survival	December 2015
NCT01083615	Custirsen	III (n = 292)	Pain palliation	December 2013
NCT01650285	Cabazitaxel with radiation	II (n = 24)	Maximum tolerated dose	January 2016
NCT01952223	Cabazitaxel with radiation	III (n = 1048)	Progression-free survival	September 2026
<i>Other disease states</i>				
NCT01576029	Early switch to cabazitaxel	II (n = 78)	PSA progression	November 2014
NCT01718353	Early switch from docetaxel to cabazitaxel and opposite sequence	II (n = 100)	PSA and circulating tumor cells	July 2015
NCT01941550	Neoadjuvant cabazitaxel	II (n = 35)	Progression free survival	August 2018
NCT01308567	Cabazitaxel versus docetaxel	III (n = 1170)	Overall survival	December 2017
NCT01978873	Early chemotherapy with curative intent	III (n = 400)	Overall survival	November 2019
<i>Supportive care</i>				
NCT01649635	G-CSF and antibiotic prophylaxis	II (n = 45)	Rate of ≥ 3 neutropenia	July 2015
G-CSF, granulocyte colony-stimulating factor; PSA, prostate-specific antigen.				

practitioners consider prophylactic G-CSF a standard of care in patients with mCRPC receiving cabazitaxel, given this population tend to be older and are at high risk of developing neutropenia and infectious complications.

Another important question is the effectiveness and tolerability of cabazitaxel combined with other therapies. Ongoing phase I/II trials are evaluating the combination of cabazitaxel with both approved therapies (e.g. carboplatin, abiraterone, mitoxantrone) and investigational agents (e.g. tasquinomid, custirsen).

An additional and critical question is whether cabazitaxel use should be limited to treatment of docetaxel-refractory mCRPC. If cabazitaxel is more potent than docetaxel, then perhaps it should be considered a first-line cytotoxic agent in mCRPC. An ongoing phase III study is randomizing patients with mCRPC to receive either docetaxel 75 mg/m<sup>2</sup> or cabazitaxel 25 mg/m<sup>2</sup> as first-line cytotoxic therapy (FIRSTANA). Intriguingly, a recent press release by the National Cancer Institute reported that, in the phase III CHARTED clinical trial, docetaxel in combination with androgen deprivation therapy in

hormone-sensitive metastatic prostate cancer was associated with a survival benefit compared with Androgen deprivation therapy (ADT) alone. This leads to speculation as to whether cabazitaxel, a more potent taxane than docetaxel, may ultimately serve to produce even better results in patients with metastatic hormone-sensitive disease.

In terms of sequencing cabazitaxel in relation to abiraterone acetate, enzalutamide or radium-223, which have each been approved for therapy after docetaxel treatment, there are no prospective data that can guide the clinician about how best to do so. Each of these therapies was studied without respect to the availability of the others. Despite emerging retrospective data to answer these questions, these attempts are speculative in nature, and we can only use clinical judgment in the short term to decide whether a patient whose condition has progressed on docetaxel should switch classes of drugs to an androgen-pathway agent or a bone-targeted therapy *versus* staying on cytotoxic chemotherapy.

## Conclusion

The clinical development of cabazitaxel has provided an important proof of principle that targeted therapy to overcome a specifically identified mechanism of resistance in the treatment of mCRPC is possible. In this case, a novel taxane was demonstrated to have clinical activity in docetaxel-resistant mCRPC. Given that mCRPC remains incurable, even with the advent of multiple new therapies, each approved drug will have a place in both extending survival and improving patient quality of life. Cabazitaxel represents a therapeutic option for men with metastatic CRPC whose condition has progressed on docetaxel and is associated with a survival advantage.

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## Conflict of interest statement

Dr. William K. Oh serves on the advisory board for Sanofi-Aventis.

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