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ADIS DRUG CLINICAL Q&A

Cabazitaxel: A Guide to Its Use in Hormone-Refractory Metastatic Prostate Cancer

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Abstract The taxane derivative cabazitaxel (Jevtana®) is approved in the USA and the EU for use in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. In the pivotal TROPIC trial, overall survival was significantly prolonged with cabazitaxel plus prednisone versus mitoxantrone plus prednisone in patients with metastatic castration-resistant prostate cancer who had progressed during or after docetaxel therapy. In addition, progression-free survival, the times to tumour progression and prostate specific antigen (PSA) progression, and tumour and PSA response rates were improved with cabazitaxel plus prednisone. Intravenous cabazitaxel had an acceptable tolerability profile, with haematological adverse events occurring most commonly, and diarrhoea being the most common nonhaematological adverse event.

Adis evaluation of cabazitaxel in hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen

What are its key clinical benefits?

Cabazitaxel plus prednisone significantly prolongs overall survival compared with mitoxantrone plus prednisone

Significantly longer progression-free survival and times to tumour or prostate specific antigen (PSA) progression than mitoxantrone plus prednisone

Significantly higher tumour and PSA response rates than mitoxantrone plus prednisone

Acceptable tolerability profile

What are its key clinical limitations?

Associated with haematological toxicity (including neutropenic deaths)

Severe hypersensitivity reactions may occur

1 What is the Rationale for Developing Cabazitaxel?

Prostate cancer is the most common form of cancer in men [1]. Although potentially curative treatment (e.g., radiotherapy and surgery) exists for patients with localized disease, the treatment of metastatic castration-resistant prostate cancer remains a significant challenge [2, 3].

Historically, mitoxantrone was often offered to patients with metastatic castration-resistant prostate cancer [3]. However, although it improved health-related quality of life and alleviated pain, mitoxantrone did not improve survival [3], highlighting the need for additional treatment options in this setting. The taxane derivative cabazitaxel

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(Jevtana®) is one such option. It is recommended by current National Comprehensive Cancer Network (NCCN) guidelines for the second-line treatment of metastatic castration-resistant prostate cancer following docetaxel failure (docetaxel plus prednisone is the preferred first-line chemotherapy treatment in patients with symptomatic metastatic castration-resistant prostate cancer) [1]. Other second-line options recommended by NCCN include abiraterone acetate, salvage chemotherapy, sipuleucel-T, mitoxantrone, docetaxel rechallenge and secondary androgen-deprivation therapy [1]. No consensus currently exists as to the best additional therapy following docetaxel failure in metastatic castration-resistant prostate cancer [1].

2 How Does Cabazitaxel Work?

Cabazitaxel is a semisynthetic taxane derivative that acts as a microtubule inhibitor [4–6]. It binds to tubulin, promoting the assembly of tubulin into microtubules and inhibiting their disassembly, which results in microtubule stabilization, the inhibition of cell division, cell cycle arrest and the arrest of tumour proliferation [5–7].

Cabazitaxel demonstrated antitumour activity against advanced human tumours xenografted in mice [8, 9]. As well as being active in docetaxel-sensitive tumours, cabazitaxel showed activity in tumour models insensitive to chemotherapy, including docetaxel [8, 9]. Cabazitaxel also penetrates the blood-brain barrier to a greater extent than docetaxel [4–6, 10].

3 For Whom is Cabazitaxel Indicated?

Cabazitaxel is approved in the USA [9] and the EU [8] for use in combination with prednisone [8, 9] or prednisolone [8] for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. Table 1 provides a summary of the USA [9] and EU [8] prescribing information for cabazitaxel.

4 What is Its Therapeutic Efficacy?

4.1 Is It More Effective than Mitoxantrone Plus Prednisone?

Phase I and/or II trials have demonstrated the potential of cabazitaxel in patients with solid tumours [7, 11–13], including prostate cancer [7]. The efficacy of combination therapy with cabazitaxel and prednisone in patients with metastatic castration-resistant prostate cancer that had progressed during or after treatment with a docetaxel-containing regimen was shown in the TROPIC trial [14]. TROPIC was a randomized, open-label, multinational, phase III trial that compared intravenous cabazitaxel 25 mg/m^2 ($n = 378$) with intravenous mitoxantrone 12 mg/m^2 ($n = 377$); both agents were administered on day 1 of a 21-day cycle in combination with a daily dose of oral prednisone 10 mg (or prednisolone if prednisone was unavailable). Treatment continued for a maximum of ten cycles, with a median six cycles administered to cabazitaxel recipients and a median four cycles administered to mitoxantrone recipients; the median duration of follow-up was 12.8 months. The vast majority of patients in TROPIC (>90 %) had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1 [14].

The median duration of overall survival (OS) [primary endpoint] was significantly longer in patients receiving cabazitaxel than in those receiving mitoxantrone in both the final efficacy analysis and an updated efficacy analysis (Table 2) [14, 15]. At 2 years, 60 cabazitaxel recipients and 31 mitoxantrone recipients were alive (odds ratio 2.10; 95 % CI 1.33, 3.33) [16].

Post hoc analysis (available as an abstract and poster) demonstrated that median OS was significantly prolonged with cabazitaxel versus mitoxantrone in the subgroup of patients with poorly differentiated histopathology ($n = 437$) [15.2 vs. 12.7 months; $p < 0.0001$], but not in the smaller subgroup of patients with well or moderately differentiated histopathology ($n = 214$) [15.5 vs. 13.3 months] [16]. Further analysis revealed that in both treatment groups, the OS duration increased as the duration of prior hormonal therapy increased; however, the OS benefit seen with cabazitaxel versus mitoxantrone was not affected by the duration of prior hormonal therapy [16].

Univariate analysis identified several variables as significant prognostic factors for OS, including an ECOG performance status of 2, measurable disease at baseline, time from the last docetaxel dose to randomization of <6 months, time from the last docetaxel dose to progression of <6 months, pain at baseline and rising prostate specific antigen (PSA) level at baseline; the OS benefit seen with cabazitaxel was maintained across these subgroups (analysis available as a poster) [17]. An ECOG performance status of 2, measurable disease at baseline, time from the last docetaxel dose to randomization of <6 months and pain at baseline remained significant ($p < 0.001$) prognostic factors for OS after multivariate analysis [17].

The median duration of progression-free survival (PFS) and the median times to tumour progression and PSA progression, but not the median time to pain progression, were significantly prolonged with cabazitaxel versus mitoxantrone (Table 2) [14].

The tumour response rate and the PSA response rate were significantly higher in cabazitaxel recipients than in

Table 1 Prescribing summary for cabazitaxel (Jevtana®) in adults with hormone-refractory metastatic prostate cancer in the USA [9] and EU [8]. Consult local prescribing information for further details

What is its approved indication?	
In combination with prednisone (USA, EU) or prednisolone (EU) for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen	
What is its dosage and administration?	
Recommended dosage	25 mg/m^2 as a 1 h IV infusion every 3 weeks plus oral prednisone (or prednisolone) 10 mg/day
Dose modification	Delay treatment until improved then reduce dosage to 20 mg/m^2 in patients with prolonged neutropenia of grade ≥3 severity despite treatment (USA, EU), febrile neutropenia (USA, EU), neutropenic infection (EU), persisting diarrhoea or diarrhoea of grade ≥3 severity despite treatment (USA, EU) or peripheral neuropathy of grade ≥2 severity (EU)
How is it available and how should it be stored?	
Available in single-use vials of 1.5 mL of concentrate containing cabazitaxel 60 mg	
Store at 25 °C (excursions permitted between 15–30 °C) [USA] or at <30 °C (EU); do not refrigerate	
What is its pharmacokinetic profile?	
Distribution	Steady-state volume of distribution: ≈4870 L
	Binding to human serum proteins: 89–92 %
Metabolism	Undergoes extensive hepatic metabolism by CYP3A4 (and to a lesser extent by CYP2C8)
Elimination	Mainly excreted in faeces (76 % of dose), with <4 % of dose excreted in urine
	Terminal elimination half-life: 95 h
How should it be used in special patient populations?	
Hepatic impairment	Do not use if bilirubin ≥1 × ULN, or AST and/or ALT ≥1.5 × ULN (USA, EU)
Renal impairment	Mild: no dosage adjustment needed (USA, EU)
	Moderate: no dosage adjustment needed (USA); use with caution (EU)
	Severe or end-stage renal disease: use with caution (USA, EU)
Elderly	No dosage adjustment needed (USA, EU)
What are the contraindications to its use?	
Neutrophil count <1,500/mm^3 (USA, EU)	
History of (severe [USA]) hypersensitivity reactions to cabazitaxel (USA, EU), other drugs formulated with polysorbate 80 (USA), other taxanes (EU) or any excipients of the formulation including polysorbate 80 (EU)	
Hepatic impairment (bilirubin ≥1 × ULN, or AST and/or ALT ≥1.5 × ULN (EU)	
Concomitant vaccination with yellow fever vaccine (EU)	
What warnings and precautions are associated with its use?[a]	
Severe hypersensitivity reactions may occur; premedication should be administered ≥30 min prior to each cabazitaxel infusion[b] (USA, EU)	
Neutropenic deaths have been reported; complete blood counts should be performed weekly during cycle 1 and then before each treatment cycle (USA, EU)	
Patients with diarrhoea should be treated with rehydration and antidiarrhoeal medication as required and electrolytes should be monitored and corrected as necessary (USA, EU)	
If renal failure occurs, the cause should be identified and the patient aggressively treated (USA, EU)	
Are there any potential drug interactions?	
CYP3A4 inhibitors	Avoid coadministration of strong CYP3A4 inhibitors (USA, EU); coadministered moderate CYP3A4 inhibitors with caution (USA, EU)
CYP3A4 inducers	Avoid coadministration of strong CYP3A4 inducers and hypericum (St John's wort) [USA, EU]
OATP1B1 substrates	Interval of 12 h before and 3 h after cabazitaxel administration recommended before administering OATP1B1 substrates (e.g. statins, valsartan, repaglinide) [EU]
Live vaccines	Avoid vaccination with live attenuated vaccines during cabazitaxel treatment (EU)

CYP cytochrome, *IV* intravenous, *OATP* organic anion transport polypeptides, *ULN* upper limit of normal

[a] The US prescribing information carries a black box warning regarding the risk of neutropenic death and severe hypersensitivity reactions

[b] Recommended premedication comprises an antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg or equivalent), a corticosteroid (dexamethasone 8 mg or equivalent) and an histamine H_2-receptor antagonist (ranitidine 50 mg or equivalent)

Table 2 Efficacy of cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in adults with metastatic castration-resistant prostate cancer. Results of the randomized, open-label, multinational TROPIC trial [14, 15]

Endpoint	Cabazitaxel + prednisone (n = 378)	Mitoxantrone + prednisone (n = 377)	Hazard ratio (95 % CI)
Primary endpoint [cut-off date][a]			
Median OS duration (months) [25 Sep 2009]	15.1**	12.7	0.70 (0.59, 0.83)
Median OS duration (months) [10 Mar 2010]	15.1**	12.7	0.72 (0.61, 0.84)
Secondary endpoints			
Median PFS duration (months)	2.8**	1.4	0.74 (0.64, 0.86)
Median time to tumour progression (months)	8.8**	5.4	0.61 (0.49, 0.76)
Median time to PSA progression (months)	6.4*	3.1	0.75 (0.63, 0.90)
Median time to pain progression (months)	11.1	Not reached	0.91 (0.69, 1.19)
Tumour response rate (% of pts)	14.4*	4.4	
PSA response rate[b] (% of pts)	39.2*	17.8	
Pain response rate[c] (% of pts)	9.2	7.7	

CI confidence interval, *OS* overall survival, *PFS* progression-free survival, *PPI* present pain intensity, *PSA* prostate specific antigen, *pts* patients

* $p \leq 0.001$, ** $p < 0.0001$ vs. mitoxantrone + prednisone

[a] The final efficacy analysis had a cut-off date of 25 Sep 2009 [14], and an updated efficacy analysis (available as an abstract) was subsequently conducted with a cut-off date of 10 Mar 2010 [15]

[b] Among pts with a baseline PSA level of ≥20 μg/L, PSA response was defined as a ≥50 % reduction in PSA level, confirmed after ≥3 weeks

[c] Among pts with a baseline median PPI score of ≥2 and/or a mean analgesic score of ≥10, pain response was defined as a reduction in median PPI score of ≥2 without an increase in analgesic score, or a ≥50 % reduction in analgesic score without an increase in the PPI score, maintained for ≥3 weeks

mitoxantrone recipients, although there was no significantly between-group difference in the pain response rate (Table 2) [14].

4.2 What Is Its Efficacy in Early-Access Programmes?

Results regarding the efficacy of cabazitaxel in metastatic castration-resistant prostate cancer that had progressed during or after docetaxel treatment are also available from early-access programmes in Spain ($n = 65$) [18], Italy ($n = 32$) [19] and Canada ($n = 61$) [20] [analyses available as abstracts and/or posters]. Patients received intravenous cabazitaxel 25 mg/mg^2 every 3 weeks plus oral prednisone 10 mg/day.

In the Spanish analysis, the median PFS duration was 4.4 months in cabazitaxel recipients; patients had received a median six cycles of cabazitaxel treatment [18]. A reduction in the PSA level of ≥50 % occurred in 64 % of patients [18].

In the Italian analysis, the median PFS duration was 8.2 months in cabazitaxel recipients; patients had received a median ten cycles of cabazitaxel treatment [19]. A reduction in the PSA level of ≥50 % occurred in 53 % of patients, a radiological response occurred in 32 % of patients and pain relief was reported in 9 of the 14 patients (64 %) who reported pain at baseline.

In the Canadian analysis, a significant ($p < 0.05$) improvement in pain (as assessed by the pain/discomfort dimension of the EQ-5D-3L) was reported with cabazitaxel [20]. 'No problem' in pain was reported by 17 % of patients at baseline and by 30 % of patients after six cycles of cabazitaxel therapy. Other EQ-5D-3L dimensions (anxiety/depression, mobility, self-care, usual activities) remained stable during cabazitaxel therapy [20].

5 What is Its Tolerability Profile?

Intravenous cabazitaxel had an acceptable tolerability profile in the TROPIC trial, with haematological adverse events being the most commonly occurring adverse events [14]. When haematological adverse events of all grades were considered, anaemia occurred in 97 % of cabazitaxel recipients versus 81 % of mitoxantrone recipients, with leukopenia occurring in 96 % versus 92 %, neutropenia occurring in 94 % versus 88 % and thrombocytopenia occurring in 47 % versus 43 % [14].

Neutropenia of at least grade 3 severity occurred in 82 % of cabazitaxel recipients, with febrile neutropenia reported in 8 % (Fig. 1) [14]. Moreover, neutropenia and its clinical consequences resulted in death in 2 % of cabazitaxel recipients and 0.3 % of mitoxantrone recipients. In the TROPIC trial, prophylactic granulocyte colony-stimulating factor (G-CSF) was not permitted during the first cycle of treatment, but could be administered in subsequent cycles after the first occurrence of neutropenia lasting ≥7 days or neutropenia complicated by fever or infection [14].

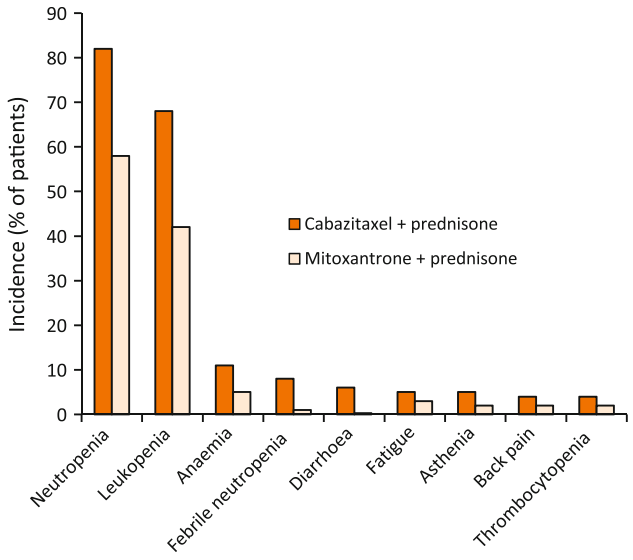

Fig. 1 Tolerability of intravenous cabazitaxel in patients with metastatic castration-resistant prostate cancer. Results of the randomized, open-label, multinational TROPIC trial in which patients received intravenous cabazitaxel plus oral prednisone ($n = 371$) or intravenous mitoxantrone plus oral prednisone ($n = 371$) [14]. Shown is the incidence of adverse events of at least grade 3 severity occurring in ≥4 % of patients in either treatment group

In terms of nonhaematological adverse events, diarrhoea (all grades) was reported in 47 % of cabazitaxel recipients versus 11 % of mitoxantrone recipients [14]. Diarrhoea was more common in patients aged >75 years and in those who had received prior radiotherapy [2]. Diarrhoea should be managed proactively [2], and cabazitaxel treatment delays and dose reductions may be necessary (Table 1).

Other nonhaematological adverse events (all grades) included fatigue (37 % of cabazitaxel recipients vs. 27 % of mitoxantrone recipients), nausea (34 % vs. 23 %), vomiting (23 % vs. 10 %), asthenia (20 % vs. 12 %), constipation (20 % vs. 15 %), haematuria (17 % vs. 4 %) and back pain (16 % vs. 12 %) [14].

The incidence of the most commonly occurring nonhaematological adverse events of at least grade 3 severity in the TROPIC trial are shown in Fig. 1 (e.g. diarrhoea, fatigue, asthenia, back pain) [14]. Grade 3 peripheral neuropathy was reported in 0.8 % of cabazitaxel recipients and 0.8 % of mitoxantrone recipients [14].

Postmarketing surveillance data (available as an abstract) from the USA indicated that the safety profile of cabazitaxel in this setting was consistent with that seen in the TROPIC trial in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel [21].

In addition, the adverse event profile of cabazitaxel in elderly patients aged ≥70 years ($n = 325$) appeared manageable, according to interim results of European early-access or compassionate-use programmes examining the efficacy of cabazitaxel in patients with metastatic castration-resistant prostate cancer that had progressed during or after docetaxel treatment (available as an abstract and poster) [22]. Compared with patients aged <70 years ($n = 421$), numerically more patients aged ≥70 years received G-CSF; however, the haematological adverse event profile of cabazitaxel in the two patient groups appeared similar.

No evidence of clinically significant prolongation of the corrected QT interval was seen in patients with advanced solid tumours who received cabazitaxel (study available as a poster) [23].

5.1 How Should Neutropenia be Managed?

Patients being treated with cabazitaxel may receive prophylactic G-CSF, in accordance with American Society of Clinical Oncology (ASCO) guidelines [24] and/or institutional guidelines, in order to reduce the risk of, or manage, neutropenic complications [8]. Primary G-CSF prophylaxis should be considered in high-risk patients (e.g., patients aged >65 years and patients with a poor performance or nutritional status, previous episodes of febrile neutropenia, extensive prior radiation ports or other serious comorbidities) [8, 9]. The cabazitaxel dose should be reduced in patients who develop febrile neutropenia or prolonged neutropenia despite appropriate treatment; cabazitaxel therapy should only be recommenced once the neutrophil count has recovered to ≥1500/mm^3 (Table 1) [8, 9].

Data supporting this approach come from an interim tolerability analysis in 919 patients enrolled in early-access or compassionate-use programmes in 30 countries (available as an abstract and poster) [25]. Patients had metastatic castration-resistant prostate cancer previously treated with docetaxel. Patients received intravenous cabazitaxel 25 mg/m^2 every 3 weeks plus oral prednisone or prednisolone 10 mg/day. In addition, G-CSF was administered according to ASCO guidelines [24], with G-CSF administered to 51 % of patients in the first treatment cycle and 61 % of patients across all cycles; prophylactic, rather than therapeutic, G-CSF was administered in the majority of these patients [25].

Of the 502 patients who had discontinued cabazitaxel at the time of the interim analysis, 135 (27 %) had discontinued because of adverse events [25]. Overall, adverse events were reported in 822 of 919 patients (89 %), with adverse events of at least grade 3 or 4 severity reported in 51 % and 24 % of patients, respectively [25].

Among cabazitaxel recipients, neutropenia (all grades) was reported in 20 % of patients, with neutropenia of grade 3–4 severity reported in 17 % and febrile neutropenia reported in 6 % [25]. Other commonly reported adverse events in cabazitaxel recipients included diarrhoea (all grades: 37 %; grade 3–4: 4 %), fatigue (all grades: 27 %; grade 3–4: 4 %), nausea (all grades: 24 %; grade 3–4: 1 %) and anaemia (all grades: 23 %; grade 3–4: 5 %).

6 What is Its Current Positioning?

Cabazitaxel is approved in the USA and EU for use in combination with prednisone [8, 9] or prednisolone [8] for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

Compared with mitoxantrone plus prednisone, cabazitaxel plus prednisone significantly prolongs OS in patients with hormone-refractory metastatic prostate cancer who have progressed during or after docetaxel therapy. In addition, PFS, the times to tumour progression and PSA progression, and tumour and PSA response rates are improved with cabazitaxel plus prednisone. Intravenous cabazitaxel has an acceptable tolerability profile, with haematological adverse events occurring most commonly, and diarrhoea being the most common nonhaematological adverse event.

There are a number of ongoing studies examining the efficacy of cabazitaxel in metastatic castration-resistant prostate cancer, including a phase III study comparing cabazitaxel with docetaxel in patients not previously treated with chemotherapy [26]. The efficacy of cabazitaxel in combination with radiotherapy is also being examined in patients with locally advanced, high-risk prostate cancer [27].

A phase I trial has demonstrated the potential of combination therapy with cabazitaxel and cisplatin in patients with advanced solid tumours [28]; cabazitaxel is also being assessed in patients with advanced solid tumours and hepatic impairment [29].

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