Chapter 3

Cabazitaxel in patients with metastatic castration-resistant prostate cancer: results of a compassionate use program in the Netherlands

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Abstract

Background: Cabazitaxel has been reimbursed as a second-line therapy for patients with metastatic castrate-resistant prostate cancer (mCRPC) in the Netherlands since 2011. Before reimbursement was available, cabazitaxel was provided through a compassionate use program (CUP). We report the results of the Dutch CUP, detailing the safety and efficacy of cabazitaxel in a routine clinical practice setting.

Methods: Safety and efficacy data of all five Dutch centers participating in the cabazitaxel CUP were collected. Safety data were collected prospectively using the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0. Overall survival (OS) and progression-free survival (PFS), time to PSA progression (TTPP), and best clinical response were evaluated retrospectively.

Results: Fifty-one patients were registered in the CUP; 49 received cabazitaxel. Forty-two of 49 patients (85.7%) had ≥2 metastatic sites. Patients received on average 6 cabazitaxel cycles (range 1-21). A dose reduction or dose delay occurred in 13 (26.5%) and 20 (40.8%) patients, respectively. Prophylactic granulocyte colony-stimulating factor (G-CSF) was used in 8 patients (16.3%). Grade ≥3 adverse events were observed in 25 patients (51.0%); 16 patients (32.7%) discontinued treatment because of treatment-emergent adverse events. Serious adverse events (SAEs) occurred in 16 (32.7%) patients; the most frequent SAEs were hematuria (4 patients (8.2%)) and urosepsis (3 patients (6.1%)). Febrile neutropenia occurred twice; no patient had grade ≥3 neuropathy. No toxicity-related mortality occurred. Median follow-up was 24.1 months. Median OS was 8.7 months (interquartile range (IQR) 6.0-15.9 months); median TTPP was 2.8 months (IQR 1.7-5.9 months).

Conclusion: In the Dutch CUP, patients with advanced mCRPC had delayed tumor progression with acceptable toxicities using cabazitaxel treatment.

Introduction

Metastatic castrate-resistant prostate cancer (mCRPC) is the second deadliest cancer in men in the United States (US), being surpassed only by lung and bronchial carcinomas.[1] A decade ago, the main therapy for patients with mCRPC consisted of mitoxantrone. However, this anthracenedione increased quality of life but not patient survival.[2] Therapy options for patients with mCRPC evolved in 2004, when docetaxel received approval as first-line therapy for this group of patients, based on two phase III clinical trials which concluded that docetaxel improved survival in patients with advanced prostate cancer.[3, 4] Although the introduction of docetaxel implemented a radical improvement in treatment options for patients with mCRPC, about 50% of these patients did not respond to docetaxel-treatment, and there were few objective responses.[3] Furthermore, all tumors that were initially targeted by docetaxel eventually developed resistance against this taxane.[5] Approximately 70% of patients with mCRPC treated with docetaxel had progressive disease during treatment or within 3 months after discontinuation. These observations required further development of therapy options for patients with docetaxel-resistant mCRPC and led to the discovery and approval of cabazitaxel as a second-line therapy in patients with mCRPC.

Cabazitaxel is a tubulin-binding taxane that suppresses microtubule dynamics in mitosis, resulting in mitotic arrest and apoptosis.[6, 7] This second-generation taxane effectively inhibited a wide variety of human and murine tumors *in vitro* and *in vivo* and was well tolerated by mice.[6] Mice with established DU-145 prostate tumors had a 100% complete regression after treatment with cabazitaxel at the maximum tolerated dose (MTD); 5 of 6 mice had a tumor-free survival of ≥133 days.[6] Cabazitaxel has poor substrate affinity for the adenosine triphosphate-dependent drug efflux pump P-glycoprotein (activated by overexpression of multidrug-resistant protein 1), which may partly contribute to the fact that cabazitaxel effectively inhibits cell lines with acquired resistance against docetaxel.[6, 7] In phase I/II studies, the recommended dose was established at 20 or 25 mg/m^2 through a 1 h intravenous infusion once every three weeks, the dose-limiting toxicity being neutropenia.[8, 9] Of the eight patients with mCRPC who received cabazitaxel treatment at doses ≤25 mg/m^2 in the phase I study, two patients had an objective partial response for ≥6 cycles, and an additional patient with mCRPC had a minor reduction in tumor size.[8]

In the subsequent TROPIC study (an open-label randomized multicenter phase III clinical trial), 755 patients with mCRPC were randomized to either mitoxantrone (12 mg/m^2 intravenously over 15-30 minutes every 3 weeks) plus prednisone (10 mg oral daily) or cabazitaxel (25 mg/m^2 intravenously over 1 h every 3 weeks) plus prednisone (10 mg oral daily).[10] All patients with mCRPC included in the study had documented disease progression during or after docetaxel treatment. Median overall survival (OS) was significantly increased in the cabazitaxel-treated group compared with the mitoxantrone-treated group (15.1 vs. 12.7 months, respectively; p<0.0001). Median OS was significantly increased in the cabazitaxel-treated group independent of the duration of androgen-deprivation therapy, suggesting that

cabazitaxel has effect in both aggressive and non-aggressive prostate tumors.[11] Furthermore, progression-free survival (PFS), defined as the first occurrence of prostate-specific antigen (PSA), radiologic or clinical progression, or death, was 1.4 months longer in the cabazitaxel-treated group (2.8 vs. 1.4 months; p<0.0001), and the median time to PSA progression (TTPP) was increased from 3.1 to 6.4 months. However, both grade ≥3 hematologic and non-hematologic adverse events had an increased incidence in cabazitaxel-treated patients. The most frequent grade ≥3 hematologic adverse events were neutropenia and leukopenia, which occurred in 303 (82%) and 253 (68%) cabazitaxel-treated patients, respectively, vs. 215 (58%) and 157 (42%) mitoxantrone-treated patients. Febrile neutropenia occurred in 28 (8%) cabazitaxel-treated patients and in five (1%) mitoxantrone-treated patients. The most frequent grade ≥3 non-hematologic adverse event was diarrhea, which occurred in 23 (6%) cabazitaxel-treated patients and in one (<1%) mitoxantrone-treated patient. In the TROPIC-study, nine (2.4%) mitoxantrone-treated patients died within 30 days of the last dose of the study drug (six of disease progression), whereas in the cabazitaxel-treated group, 18 (4.9%) patients died within 30 days of the last dose (none of disease progression). The most frequent causes of mortality within 30 days of the last dose of the study drug were related to neutropenia and its complications, cardiac events, and renal failure.

The clinical benefit for patients with mCRPC in the TROPIC study led to the approval of cabazitaxel for treatment of mCRPC in the US in June 2010.[12] The European Medicines Agency approved cabazitaxel for mCRPC treatment in March 2011; later in 2011, the taxane was reimbursed by insurance companies in the Netherlands. Pending final registration of cabazitaxel, a compassionate use program (CUP) was established in the Netherlands and 25 other countries in 2010 to allow access to cabazitaxel for patients with mCRPC and to record overall safety. These programs have been introduced to facilitate the availability of new treatments that are not yet reimbursed for patients with a severe disease when no satisfactory alternative is available and when it is expected that the new medicine will be approved by official authorities in the near future. Recruitment for this CUP was terminated in the Netherlands in June 2011 as cabazitaxel would be reimbursed. In this study we report the safety and efficacy of cabazitaxel in patients with mCRPC as recorded in the Dutch CUP to give an indication of the experience with cabazitaxel in a routine clinical setting.

Patients and Methods

Patients

Patients in five Dutch medical centers were included. Patients were eligible for cabazitaxel treatment if they had mCRPC and documented disease progression during or after treatment with a docetaxel-containing regimen. Patients needed to be surgically or medically castrated; be ≥ 18 years; have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; have a life expectancy of ≥3 months; and have adequate bone marrow, liver, and

renal functions. Patients were excluded from participation if they had received previous radiotherapy to ≥40% of the bone marrow, previous radionuclide therapy, or if they had received anticancer therapy within four weeks of enrollment. Patients were also excluded when they presented with grade ≥2 peripheral neuropathy, grade ≥2 stomatitis, an infection treated with systemic antibiotic or antifungal medication, or known brain or leptomeningeal involvement. Other criteria that excluded patients from participation were a history of a grade ≥3 hypersensitivity reaction to docetaxel, polysorbate 80-containing medications or predniso(lo)ne, an active cancer other than mCRPC, an uncontrolled severe illness or medical condition, concurrent or planned treatment with potent inhibitors or inducers of cytochrome P450 3A4/5, participation in a clinical trial with any investigational drug, and reproductive potential without implementation of an accepted and effective method of contraception.

Study design

This study is an analysis of the treatment of patients with mCRPC with cabazitaxel through the CUP. While patients are treated within the CUP, they are closely monitored to assess the safety of the new medicine. Because of the nature of the study, it was an ambispective multicenter observational study. Safety data were collected prospectively; efficacy data were collected retrospectively. The study was approved by the institutional ethics committees, and written informed consent was obtained from all participants.

Treatment

All patients initially received 25 mg/m^2 cabazitaxel for 1 h intravenously on day 1 of a 21-day cycle, as well as 10 mg oral prednisone or prednisolone daily. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was considered in patients with high-risk clinical features for febrile neutropenia as described by European Organisation for Research and Treatment of Cancer (EORTC) guidelines, such as previous episodes of (febrile) neutropenia, age > 65 years, poor performance and/or nutritional status, extensive previous radiation, and/or serious comorbidities.[13] G-CSF was administered when the physician estimated the chance for febrile neutropenia to be ≥ 20%. Patients were pretreated intravenously with an antihistamine (clemastine 1 mg), a corticosteroid (dexamethasone 8 mg or equivalent), and an H2 antagonist (ranitidine or equivalent) at least 30 minutes before cabazitaxel treatment. Additional oral or intravenous anti-emetic prophylaxis was administered at the physician's discretion. The recommended additional anti-emetic prophylaxis was metoclopramide. Patients who experienced grade ≥3 nausea and/or vomiting received more aggressive anti-emetic prophylaxis, namely, ondansetron. However, physicians were allowed to diverge from this protocol. Therefore, four patients received granisetron as anti-emetic prophylaxis. Furthermore, ondansetron was administered immediately if limited effect was expected from metoclopramide in an individual patient or if (severe) nausea and/or vomiting was

expected based on previous toxicities from other chemotherapy (docetaxel).
The protocol required a treatment delay when patients had an absolute neutrophil count of ≤1500/mm^3, a thrombocyte count of ≤75000/mm^3, grade ≥3 non-hematologic toxicities (except alopecia and nail changes) that had not recovered to the baseline, an aspartate aminotransferase or alanine aminotransferase concentration >1.5 times the upper limit of normal, and/or a bilirubin concentration higher than the upper limit of normal. If patients had not recovered from these toxic effects after two weeks of treatment delay, treatment was terminated. The protocol required a dose reduction to 20 mg/m^2 after an episode of grade ≥3 neutropenia and/or febrile neutropenia, grade 4 thrombocytopenia, grade ≥3 vomiting despite appropriate anti-emetic prophylaxis, grade ≥3 diarrhea or persisting diarrhea despite appropriate medication, grade ≥3 stomatitis, grade 2 peripheral neuropathy (patients with grade ≥3 peripheral neuropathy were withdrawn from treatment), liver abnormalities as described earlier, a creatinine clearance between 40 and 60 ml/min (patients with a creatinine clearance <40 ml/min were withdrawn from treatment), and any other grade ≥3 toxicity (except for alopecia and nail changes) that had improved to grade 2 or better. Dose re-escalation or further dose reductions were not allowed.
Although cabazitaxel treatment was discontinued after a maximum of ten cycles in the TROPIC study, physicians and patients were allowed to decide to continue treatment beyond ten cycles in the CUP if patients responded well to cabazitaxel treatment. Treatment was discontinued based on the patient's or physician's decision, adverse events, disease progression, and/or death. Patients were allowed to discontinue treatment at any time for any reason.

Outcome measures
Every patient underwent an extensive medical assessment before initiation of cabazitaxel treatment. This assessment included the collection of data regarding demographics (date of birth), vital signs, height, weight, ECOG performance status, history of prostate cancer, findings during physical examination, and hematologic (neutrophil and thrombocyte count, hemoglobin) and biochemical laboratory diagnostics (liver function, kidney function, and serum PSA concentration, among others). Furthermore, CT and bone scans were obtained if no recent test results were available. Before each cabazitaxel administration, new and existing symptoms were assessed and graded, physical examinations were performed, liver and renal functions were checked, a hematologic assessment was done, the serum PSA level was determined, and when clinically indicated, other diagnostic tests (e.g., CT, MRI, radiography, bone scans, and electrocardiograms) were performed. When cabazitaxel treatment was terminated, vital signs (weight, ECOG performance status) were registered and blood tests were performed. Prostate cancer progression, subsequent treatments, and OS were followed up until death or until the last date the patient was known to be alive before February 21, 2013.

OS was calculated as the number of days between the first day of cabazitaxel treatment and death or censoring. Other efficacy parameters were TTPP, PFS, best clinical response, and PSA response. TTPP and PSA response were considered the most reliable efficacy parameters, because serum PSA levels had been determined in patients every three weeks, whereas other diagnostic tests, such as radiologic assessments, were performed at the physician's discretion at random time points.

TTPP was calculated from the first day of cabazitaxel treatment according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) recommendations.[14] In patients who had an initial PSA decrease, PSA progression was defined as an increase of at least 25% over the nadir PSA concentration. In patients with no decline from the baseline PSA level, PSA progression was defined as an increase of at least 25% over the nadir PSA concentration for a duration of ≥12 weeks of treatment. Furthermore, a patient's TTPP was not determined if a different treatment was started before PSA progression was measured or if >3 months elapsed between two subsequent PSA measurements.

To report PSA-based outcomes, waterfall plots were used as recommended by the PCWG2.[14] First, the maximum PSA decrease during cabazitaxel treatment was assessed; if the PSA did not decrease at all, the maximum PSA level during cabazitaxel treatment was assessed instead. Second, the PSA change after 4 cycles was assessed.

PFS was defined as the number of months between initiation of cabazitaxel treatment and the first date of progression as measured by PSA progression (using the same criteria as for TTPP), tumor progression (either from increased measurable lesions or from increased lesions on CT/MRI/X-ray/bone scans), symptomatic progression, and/or death. Because tumor measurements were performed at the physician's discretion, in no patient was PFS based solely on tumor progression, i.e., patients with radiologic disease progression always had clinical progression or PSA progression as well. Furthermore, some patients discontinued cabazitaxel treatment because of symptoms and PSA progression, whereas, according to the definition of PCWG2, this progression may have been caused by a flare.[14] Therefore, the PFS could not be determined in these patients.

The best clinical response was considered progressive disease when both serum PSA levels were continuously increased compared with the baseline serum PSA level, PSA levels had a rising trend, and overall, patients did not have an improved condition. A partial response was defined as a PSA decrease of ≥50% compared with the baseline in at least two separate PSA measurements three weeks apart and an improvement in the patient's symptoms. Furthermore, if measurable lesions had decreased in size, it was considered a partial response as well, regardless of serum PSA levels or a change in symptoms.

Patients were intensively monitored for adverse events throughout the study by physician visits and diagnostic tests such as blood tests and electrocardiograms. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[15] Adverse events could result in the addition of medication to

treat or prevent the adverse events, dose reduction, dose delay, or withdrawal from the study. All adverse events from the onset of treatment until 30 days after the last cabazitaxel administration were recorded.

Statistical analyses

All analyses were performed with the study population that received at least one dose of cabazitaxel. Microsoft Excel was used to calculate the median, interquartile range (IQR), range, mean and standard deviation (SD) for patient characteristics, treatment characteristics and G-CSF use. IBM SPSS Statistics (version 20) was used for the statistical analyses of efficacy parameters. OS, TTPP, and PFS were analyzed using the Kaplan-Meier method. OS data were censored at the last date the patient was known to be alive; PFS data were censored at the last date the disease state of the patient was assessed if no disease progression had occurred. Log-rank tests were used to calculate differences in TTPP and OS between groups that had been stratified based on age, body mass index (BMI), time between prostate cancer and mCRPC diagnosis, initial Gleason score, ECOG performance score at the start of cabazitaxel treatment, PSA levels at the start of cabazitaxel treatment, previous docetaxel therapy, and pretreatment with abiraterone/enzalutamide, as well for calculating the significance of the difference between median received cabazitaxel cycles.

Role of outside organizations

Sanofi-Aventis provided a database with all treatment-emergent adverse events (TEAEs) registered. The authors had full access to safety data collected in the CUP by Sanofi-Aventis; analyses were performed independently from Sanofi-Aventis. The decision to submit the report for publication was made by the chief investigators (MDW and HG), who wrote the manuscript with input from the other authors. Sanofi-Aventis reviewed the final manuscript before submission.

Results

Patients and treatment

Between July 28, 2010 and April 27, 2011, cabazitaxel treatment was initiated in 49 of 51 patients selected in five hospitals to participate in the CUP. Two patients withdrew from the CUP between selection and treatment initiation, as the result of being unable to visit the hospital because of a deteriorating condition. Data from these two patients were not included in the analyses, because the aim of our study was not to perform an intention-to-treat analysis but to determine the safety and efficacy of cabazitaxel in Dutch clinics. Median age of the 49 patients who received at least one administration of cabazitaxel was 64.6 years (IQR 58.6-70.0); three patients were older than 75 years (Table 1). Most patients (71.4%) had an ECOG performance status of 1 during selection; 12 patients (24.5%) had an ECOG

performance status of 2. A majority of patients (85.7%) had at least 2 sites of metastases; the two most frequent metastatic sites were bone and lymph nodes. Lung and liver metastases had been diagnosed in 6 (12.2%) and 7 (14.3%) patients, respectively. Twenty-four patients (49.0%) had received 2 or more chemotherapy regimens, and 10 patients (20.4%) had received abiraterone (10.2%), enzalutamide (8.2%), and/or immunotherapy (ipilimumab/CNTO95) (4.1%) before cabazitaxel. Patients had received a median dose of 750 mg/m^2 (IQR 450-900 mg/m^2) docetaxel during the last docetaxel regimen. For patients whose disease progressed after the last docetaxel dose, median time from last docetaxel administration to disease progression was 3.22 months (IQR 1.36-6.87 months); 9 patients (18.4%) had disease progression during docetaxel treatment, whereas 11 patients (22.4%) had progressive mCRPC >6 months after the last dose of docetaxel. Before treatment initiation, the median serum PSA level was 355.5 ng/ml (IQR 123.0-1515.4 ng/ml) (Table 1). All but 1 patient (98.0%) had an initial PSA concentration ≥20 ng/ml.

Patients completed a median of 6 cycles (range 1-21 cycles) of cabazitaxel treatment in 126 days (range 21-469 days) (Fig. 1, Table 2). Nine patients (18.4%) completed 10 cycles of cabazitaxel treatment. Twelve patients (24.5%) required a dose reduction during the first 10 cycles; 1 additional patient required a dose reduction at the 20th cycle (Table 2). Seven patients needed dose reduction only at cycle 8 or higher; furthermore, the majority of patients (n=9) who needed a dose reduction had a dose reduction during their last or second to the last cycle (data not shown). Twenty patients (40.8%) required a dose delay (Table 2).

G-CSF was administered for prophylactic use to 8 patients (16.3%) for a total of 49 cycles. These eight patients completed a median number of 9.0 cabazitaxel cycles (IQR 7.5-10.0); the median number of cabazitaxel cycles in patients not treated with G-CSF was 5.0 (IQR 4.0-8.0).

After discontinuation of cabazitaxel treatment, 26 patients started other second-line systemic therapies. Twenty-three patients were treated with abiraterone acetate, two patients with docetaxel, and three patients with mitoxantrone. Three patients were treated with ipilimumab or placebo in a study setting, and four patients were treated with enzalutamide. Finally, three patients received a second cabazitaxel regimen after treatment with abiraterone acetate.

Safety

All patients reported TEAEs during treatment; 46 (93.9%) patients had adverse events possibly related to cabazitaxel treatment, as assessed at the start of each cabazitaxel cycle (Table 3). Although a serious adverse event (SAE) occurred in 16 (32.7%) patients, none of these adverse events resulted in patient death. Grade ≥3 events occurred in 25 (51.0%) patients; grade 4 events occurred in five (10.2%) patients. Sixteen (32.7%) patients discontinued treatment because of TEAEs.

Table 1. Baseline characteristics of patients treated with cabazitaxel via the Dutch CUP (n=49)

Age		
Mean [years (SD)]	63.6	(8.1)
Median [years (IQR)]	64.6	(58.6-70.0)
Patients <65 years	26	(53.1%)
Patients ≥75 years	3	(6.1%)
Performance status at the start of therapy		
ECOG 0	2	(4.1%)
ECOG 1	35	(71.4%)
ECOG 2	12	(24.5%)
Extent of metastatic disease		
Number of metastatic lesions		
0	0	(0%)
1	7	(14.3%)
≥2	42	(85.7%)
Localization of metastases		
Local recurrence	23	(46.9%)
Regional lymph node	17	(34.7%)
Distant lymph node	24	(49.0%)
Bladder	6	(12.2%)
Pelvis	13	(26.5%)
Bone	47	(95.9%)
Lung	6	(12.2%)
Liver	7	(14.3%)
Bone marrow	4	(8.2%)
Mediastinum	4	(8.2%)
Other	7	(14.3%)
Previous mCRPC therapy		
Number of chemotherapy regimens		
1	25	(51.0%)
≥2	24	(49.0%)
Other mCRPC therapy (abiraterone acetate, enzalutamide and/or immunotherapy)	10	(20.4%)
Docetaxel use		
Number of previous docetaxel regimens		
Mean (SD)	1.1	(0.3)
Median (range)	1.0	(1-3)
Cumulative dose of last docetaxel administration (mg/m²)		
Mean (SD)	742.50	(358.58)
Median (IQR)	750	(450-900)
Disease progression relative to docetaxel administration		
<0 (during treatment)	9	(18.4%)
<3 months since last dose	17	(34.7%)
≥3-<6 months since last dose	12	(24.5%)
≥6 months since last dose	11	(22.4%)
Median time from last docetaxel dose to disease progression [months (IQR)]	3.22	(1.36-6.87)
Serum PSA concentration (ng/ml)		
Median (IQR)	355.5	(123.0-1515.4)
≥20 ng/ml	48	(98.0%)

Data are number of patients (%) if not specified otherwise. ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PSA, prostate-specific antigen; SD, standard deviation

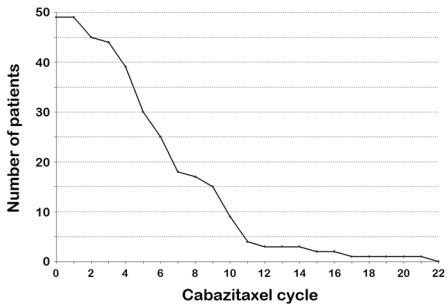

Figure 1. Cabazitaxel treatment in the Dutch CUP population. The graph displays the number of patients treated at cycle n.

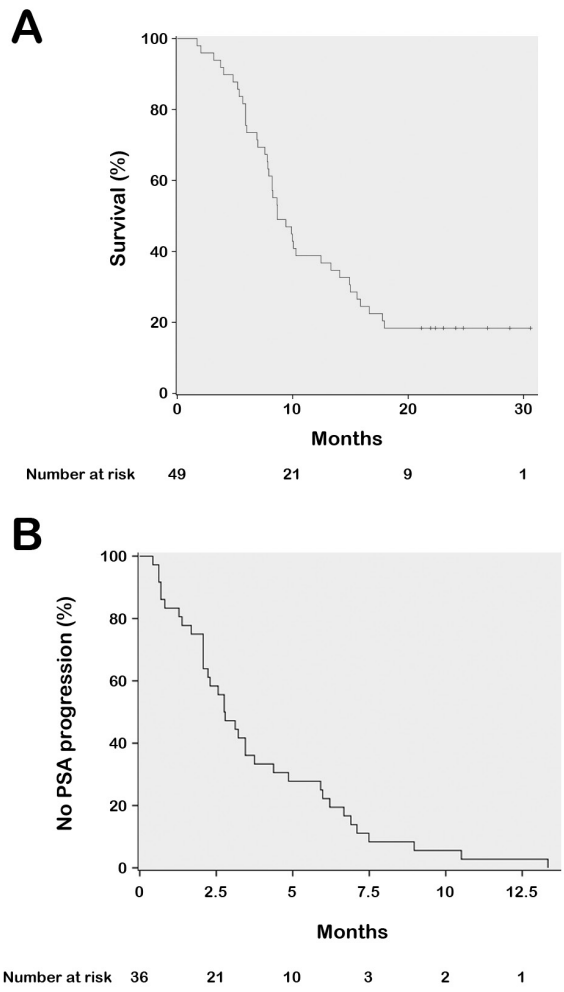

Figure 2. Kaplan-Meier estimates of (A) overall survival (OS) and (B) time to PSA progression (TTPP) in the Dutch cabazitaxel treated CUP population.
Vertical bars on the curves display censored observations.

All grade ≥3 TEAEs and SAEs, as well as grade 1 or 2 events that occurred in ≥2 patients, are listed in Table 3. The most frequent TEAE was fatigue, which occurred in 30 (61.2%) patients; grade ≥3 fatigue occurred in five (10.2%) patients. Other non-hematologic grade ≥3 TEAEs that were reported in at least two patients, were urosepsis (6.1%), bone pain (6.1%), paraplegia (4.1%), pulmonary embolism (4.1%), urinary tract infections (4.1%) and a decreased appetite (4.1%). The most frequent reported non-hematologic SAEs were hematuria and urosepsis, which occurred in 4 (8.2%) and 3 (6.1%) patients, respectively. One patient experienced grade 3 hematuria; this patient had received multiple fractions of radiation (3 × 8Gy and, 4 × 5Gy) to the pelvic region before cabazitaxel therapy. Two of four patients with grade 2 hematuria had received radiation therapy at an earlier stage as well. A grade ≥3 cardiac disorder (myocardial infarction) and diarrhea each occurred in one patient. Other frequently reported non-hematologic adverse events (all grades) were nausea (44.9%), diarrhea (40.8%), vomiting (26.5%) and malaise (20.4%) (Table 3). Grade 1 or 2 peripheral neuropathy was reported in nine patients (18.4%). Eleven patients (22.4%) had a weight loss of ≥5% of their total body weight.

Hematologic adverse events occurred in 17 (34.7%) patients. Of all cabazitaxel-treated patients with mCRPC, six patients (12.2%) experienced grade ≥3 hematologic adverse events, of which grade ≥3 (febrile) neutropenia and anemia occurred most frequently (4.1%). Seven hematologic SAEs were reported: anemia (twice), febrile neutropenia (twice), neutropenic infection, neutropenic sepsis, and hemorrhagic anemia.

Efficacy

Median follow-up was 24.1 months (IQR 22.4-26.9 months). At the cutoff date for the final analysis, 40 patients had died. Kaplan-Meier analysis of OS is displayed in Figure 2A. Median OS was 8.7 months (IQR 6.0-15.9 months); mean OS was 12.9 months (95% Confidence Interval (CI) 10.3-15.5 months) (Fig. 2A, Table 4). Fourteen patients (28.6%) had continuous progressive disease despite cabazitaxel treatment; nine patients (18.4%) had a partial response. Hence, disease control (partial response plus stable disease) was established in 35 patients (71.4%). In these 35 patients, median OS was 13.3 months (IQR 7.9 months-undetermined); mean OS was 15.6 months (95% CI 12.5-18.8 months).

TTPP was determined in 36 patients (Fig. 2B, Table 4). Mean TTPP was 3.8 months (95% CI 2.8-4.7 months); median TTPP was 2.8 months (IQR 1.7-5.9 months). Strikingly, the two patients with the longest TTPP (13.3 and 10.5 months) had received the most cabazitaxel cycles (21 and 14, respectively). The two patients, in whom cabazitaxel treatment was discontinued after ten cycles solely because of completion of ten cycles, had a TTPP of 9.0 and 7.5 months. This suggests that it might be clinically beneficial to continue treatment beyond ten cycles when there are no other indicators to stop cabazitaxel treatment; this needs to be investigated in more detail.

Predictive and prognostic factors for response to cabazitaxel treatment were determined.

Table 2. Treatment characteristics in cabazitaxel-treated patients (n=49)

Duration of treatment	
Number of treatment cycles	
Mean (SD)	6.39 (3.96)
Median (range)	6 (1-21)
Number of patients that completed ≥10 cycles	9 (18.4%)
Treatment time (days)	
Mean (SD)	144 (88)
Median (range)	126 (21-469)
Number of patients with a treatment delay	20 (40.8%)
Number of patients with a dose reduction	13 (26.5%)
dose reduction ≤cycle 10	12 (24.5%)

Data are number of patients (%) unless specified otherwise. SD, standard deviation

Table 3. Adverse events reported during cabazitaxel treatment

Patients with possibly related TEAE	46 (93.9%)
Patients who discontinued treatment due to TEAE	16 (32.7%)
Patients with hematological grade ≥3 adverse event	6 (12.2%)
Patients with ≥5% weight loss	11 (22.4%)
Patients with any grade 4 adverse event	5 (10.2%)
Patients with any grade 5 adverse event	0

	grade 3 or 4	SAE	all grades
Any adverse event	25 (51.0%)	16 (32.7%)	49 (100%)
HEMATOLOGICAL ADVERSE EVENT			
Anemia	2 (4.1%)	2 (4.1%)	14 (28.6%)
Hemorrhagic anemia	1 (2.0%)	1 (2.0%)	1 (2.0%)
Neutropenia	2 (4.1%)	2 (4.1%)	3 (6.1%)
Febrile neutropenia	2 (4.1%)	2 (4.1%)	2 (4.1%)
Leukopenia	1 (2.0%)	0	3 (6.1%)
Thrombocytopenia	1 (2.0%)	0	2 (4.1%)
NON-HEMATOLOGICAL ADVERSE EVENT			
Fatigue	5 (10.2%)	0	30 (61.2%)
Bone pain	3 (6.1%)	1 (2.0%)	12 (24.5%)
Urosepsis	3 (6.1%)	3 (6.1%)	3 (6.1%)
Decreased appetite	2 (4.1%)	0	7 (14.3%)
Urinary tract infection	2 (4.1%)	0	5 (10.2%)
Paraplegia	2 (4.1%)	2 (4.1%)	2 (4.1%)
Pulmonary embolism	2 (4.1%)	2 (4.1%)	2 (4.1%)
Nausea	1 (2.0%)	0	22 (44.9%)
Diarrhea	1 (2.0%)	0	20 (40.8%)
Vomiting	1 (2.0%)	0	13 (26.5%)
Back pain	1 (2.0%)	0	6 (12.2%)
Hematuria	1 (2.0%)	4 (8.2%)	5 (10.2%)
Spinal cord compression	1 (2.0%)	2 (4.1%)	2 (4.1%)
Myocardial infarction	1 (2.0%)	1 (2.0%)	1 (2.0%)
Hypocalcemia	1 (2.0%)	0	1 (2.0%)
Duodenal ulcer hemorrhage	1 (2.0%)	1 (2.0%)	1 (2.0%)
Colitis	1 (2.0%)	0	1 (2.0%)
Hydronephrosis	1 (2.0%)	0	1 (2.0%)
Malaise	0	0	10 (20.4%)

Pyrexia	0	1	(2.0%)	8	(16.3%)
Dehydration	0	1	(2.0%)	1	(2.0%)
Diplopia	0	1	(2.0%)	1	(2.0%)
Peripheral neuropathy	0	0		9	(18.4%)
Pain in extremity	0	0		7	(14.3%)
Arthralgia	0	0		6	(12.2%)
Constipation	0	0		5	(10.2%)
Headache	0	0		5	(10.2%)
Muscle spasms	0	0		4	(8.2%)
Cough	0	0		4	(8.2%)
Rectal hemorrhage	0	0		3	(6.1%)
Dysgeusia	0	0		3	(6.1%)
Peripheral sensory neuropathy	0	0		3	(6.1%)
Peripheral oedema	0	0		3	(6.1%)
Abnormal hepatic function	0	0		2	(4.1%)
Nasopharyngitis	0	0		2	(4.1%)
Dyspnoea	0	0		2	(4.1%)
Epistaxis	0	0		2	(4.1%)
Oropharyngeal pain	0	0		2	(4.1%)
Groin pain	0	0		2	(4.1%)
Muscular weakness	0	0		2	(4.1%)
Musculoskeletal chest pain	0	0		2	(4.1%)
Musculoskeletal pain	0	0		2	(4.1%)
Musculoskeletal stiffness	0	0		2	(4.1%)
Urinary retention	0	0		2	(4.1%)
Influenza-like illness	0	0		2	(4.1%)

Data are number of patients (%). Toxic effects were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v 3.0). All adverse events that occurred in at least two patients are listed, as well as all grade 3 or 4 adverse events and SAEs. TEAE, treatment-emerging adverse event; SAE, serious adverse event

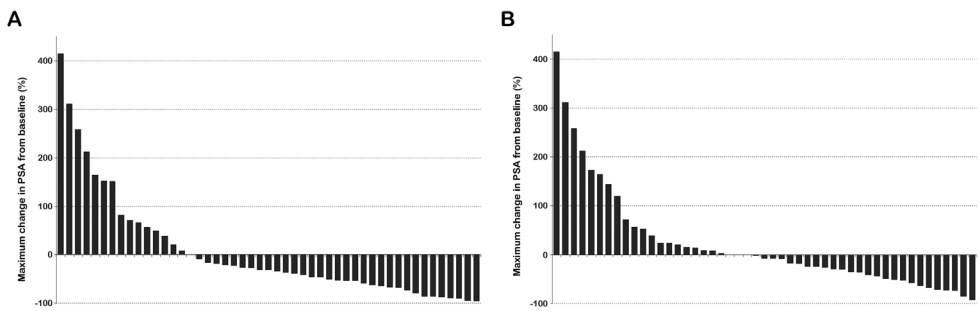

Figure 3. Waterfall plots showing (A) the maximal change in serum PSA levels from baseline during/after cabazitaxel therapy before initiation of another mCRPC treatment; (B) the change in serum PSA levels from baseline after four cabazitaxel cycles.

If patients had been treated for less than 4 cycles, the serum PSA level during/after the last cabazitaxel cycle was used.

Age, BMI, time between prostate cancer and mCRPC diagnosis, initial Gleason score, and ECOG performance score did not significantly influence the clinical outcome for cabazitaxel-treated patients (Table 4). However, patients with a PSA <500 ng/ml at the start of treatment had a longer OS than patients with an initial PSA level of ≥500 ng/ml (10.1 months vs. 7.9 months; p=0.016). Patients who had received <10 cycles of docetaxel treatment had a significantly decreased median TTPP (2.8 vs. 3.5 months) and OS (7.8 vs. 10.0 months) compared with patients who had received ≥10 docetaxel cycles (p=0.049 and p=0.015, respectively) (Table 4). Furthermore, ten of the twelve patients (83.3%) who had a TTPP >4 months had received ≥10 cycles of docetaxel before cabazitaxel treatment, whereas four of the nine patients (44.4%) who had a TTPP <2 months, had received ≥10 docetaxel cycles before cabazitaxel treatment (data not shown). The number of cabazitaxel cycles received was not significantly different between patients who had received <10 cycles and those who had received ≥10 docetaxel cycles, because the median number of cabazitaxel cycles was 5 and 6, respectively (p=0.163). Similarly, the percentage of patients who discontinued treatment because of adverse events did not differ between the two groups (30.0% and 27.6%, respectively; p=0.858). Patients pretreated with abiraterone and/or enzalutamide had a decreased OS (5.9 vs. 10.0 months; p=0.027) (Table 4). The median TTPP tended to differ significantly as well (2.1 vs. 3.2 months; p=0.052). Between these groups of patients, the median number of cabazitaxel cycles was not significantly different (4 vs. 6; p=0.065).

PFS was similar to TTPP, because disease progression was first indicated by a rising PSA level in most patients. PFS was determined in 46 patients. Median PFS was 2.8 months (IQR 1.7-4.9 months), and mean PFS was 3.8 months (95% CI 2.8-4.7 months) (Table 4).

Figure 3 displays waterfall plots of the two analyses of PSA progression as recommended by the PCWG2.[14] Fifteen patients had a continuous increase in PSA levels. One patient had a PSA measurement at the start of the cabazitaxel treatment only because this patient had SAEs during the first cycle and did not have his PSA measured afterwards. Six patients had an initial PSA decrease, but had their serum PSA levels increase to the baseline PSA level or higher during the first four cycles. The remaining 27 patients had a decrease in PSA levels that was sustained during the first four cycles of cabazitaxel treatment. Of these patients, 19 had a PSA decrease of ≥25% for at least four cycles. The maximum decrease in PSA was 92.9%; this patient's PSA level decreased from 3669 ng/ml to 172.4 ng/ml during six cabazitaxel cycles. Despite the PSA decrease, the patient discontinued treatment because of a deteriorating condition. Seven months after discontinuation of cabazitaxel, his PSA level had increased to 5000 ng/ml.

Finally, we studied whether patients who had a decrease in PSA levels by at least 25% and 50% compared with the baseline PSA serum concentration, had an increased OS and TTPP compared with patients who did not have such a PSA response. Patients who had at least a 25% decrease in PSA after four cycles of cabazitaxel had a median TTPP and OS of 6.2 (IQR 4.4-7.5) and 16.6 (9.4-undetermined) months, respectively, compared with 2.1 (0.8-

Table 4. Efficacy parameters of cabazitaxel treatment

Overall survival (OS) (n=49)		
Mean [months (95% CI)]	12.9	(10.3-15.5)
Median [months (IQR)]	8.7	(6.0-15.9)
Time to PSA progression (TTPP) (n=36)		
Mean [months (95% CI)]	3.8	(2.8-4.7)
Median [months (IQR)]	2.8	(1.7-5.9)
Progression-free survival (PFS) (n=46)		
Mean [months (95% CI)]	3.8	(2.8-4.7)
Median [months (IQR)]	2.8	(1.7-4.9)
Best response (n=49)		
Progressive disease (%)	14	(28.6%)
Partial response (%)	9	(18.4%)
OS in patients who responded to cabazitaxel (n=35)		
Mean [months (95% CI)]	15.6	(12.5-18.8)
Median [months (IQR)]	13.3	(7.9-N/A)

Patient characteristic	**TTPP**				**OS**			
	#	**Median (IQR)**			**#**	**Median (IQR)**		
age <65 years	20	3.2	(1.4-4.9)	p=0.458	26	8.3	(5.9-17.8)	p=0.731
age ≥65 years	16	2.6	(2.1-5.9)		23	9.9	(7.6-15.9)	
BMI <25	10	2.8	(2.1-5.9)		15	9.9	(6.9-N/A)	
BMI 25-30	20	2.6	(1.4-4.9)	p=0.972	24	8.2	(5.7-14.9)	p=0.616
BMI >30	5	3.5	(2.1-4.4)		9	13.3	(8.7-15.9)	
time to mCRPC <12 months	8	2.1	(0.7-3.1)	p=0.282	11	7.6	(5.9-10.1)	p=0.121
time to mCRPC ≥12 months	28	2.8	(2.1-6.0)		38	9.9	(6.0-17.8)	
Gleason score <8	10	2.8	(2.2-3.5)	p=0.407	12	12.5	(6.0-15.6)	p=0.750
Gleason score 8-10	16	2.5	(2.1-6.7)		22	9.4	(8.2-17.9)	
ECOG <2	28	2.8	(2.1-6.0)	p=0.118	37	10.0	(7.6-16.6)	p=0.347
ECOG ≥2	8	1.7	(0.7-3.1)		12	7.0	(4.8-9.4)	
PSA <500 ng/ml	23	3.1	(0.8-5.9)	p=0.655	26	10.1	(7.9-N/A)	p=0.016
PSA ≥500 ng/ml	13	2.6	(2.1-6.0)		23	7.9	(5.7-14.1)	
Docetaxel <10 cycles	15	2.8	(1.4-3.5)	p=0.049	19	7.8	(5.9-10.3)	p=0.015
Docetaxel ≥10 cycles	21	3.5	(2.1-6.9)		30	10.0	(7.9-N/A)	
prior treatment with abiraterone/ enzalutamide	7	2.1	(1.3-3.1)	p=0.052	8	5.9	(5.4-8.3)	p=0.027
no prior treatment with abiraterone/ enzalutamide	29	3.2	(2.1-6.2)		41	10.0	(7.6-17.8)	

The IQR could not be determined if >25% of patients were alive at the cutoff date (N/A). #, number of patients; IQR, interquartile range; BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

2.8) and 7.9 (IQR 5.9-10.0) months in the rest of the patients (p<0.001). Patients who had at least a 50% decrease in PSA had a median TTPP and OS of 6.9 (IQR 5.9-9.0) and 16.6 (15.0-undetermined) months, respectively, compared with 2.3 (1.4-3.5) and 8.3 (IQR 5.9-

13.3) months in the rest of the patients (p=0.017 and p=0.024, respectively). However, between patients who had a 25% to 50% decrease and those who had a >50% decrease in PSA, the TTPP and OS did not differ significantly (p=0.854 and p=0.644, respectively).

Discussion

In the TROPIC study, patients with mCRPC treated with cabazitaxel had an increased PFS and OS compared with mitoxantrone-treated patients irrespective of the aggressiveness of the tumor.[10, 11] However, both grade ≥3 hematologic and non-hematologic adverse events had an increased incidence in cabazitaxel-treated patients. Since the completion of this phase III study, several studies with cabazitaxel reported fewer high-grade adverse events.[16-18] In the TROPIC study, grade ≥3 adverse events occurred in 82% of all patients; adverse events were assessed on a weekly basis.[10] Of all patients included in the German CUP, grade ≥3 TEAEs occurred in 30.6% of patients.[19] In our study, grade ≥3 adverse events occurred in 51.0% of patients. Similarly, grade ≥3 neutropenia, leukopenia, and diarrhea were reported in 82%, 68%, and 6% of patients in the TROPIC study, respectively.[10] Grade ≥3 neutropenia, leukopenia, and diarrhea were reported in 7.2%, 9.0%, and 0.9% of patients of the German CUP, respectively.[19] Preliminary data of cabazitaxel-use in patients with mCRPC through a CUP in Italy reported grade ≥3 neutropenia, leukopenia, and diarrhea in 48.9%, 25.6%, and 1.1% of patients, respectively.[16] In an expanded access program (EAP) in Spain grade ≥3 neutropenia and diarrhea occurred in 24% and 1.5% of cabazitaxel-treated patients with mCRPC, respectively.[17] All three studies assessed adverse events once every three weeks. In line with these results, grade ≥3 neutropenia, leukopenia and diarrhea occurred in 4.1%, 2.0%, and 2.0% of patients who participated in the Dutch CUP, respectively. The decreased number of hematologic adverse events may be partially result from the use of prophylactic G-CSF in high-risk patients according to EORTC guidelines[13], whereas in the TROPIC study no prophylactic G-CSF was allowed. Furthermore, in the TROPIC study TEAEs were assessed weekly, whereas in the CUPs and docetaxel phase III study, TEAEs were assessed once every three weeks, simulating the clinical practice setting.[3] Most of the TEAEs that were missed by doing an assessment every three weeks instead of weekly, were asymptomatic TEAEs that disappeared within three weeks (such as neutropenia without fever), and thus were not clinically relevant. Finally, patients and/or doctors could have decided to discontinue cabazitaxel treatment at an earlier stage because of the availability of abiraterone acetate as an alternative drug for patients with mCRPC, preventing the onset of grade ≥3 adverse events. This latter is confirmed by the lower percentage of patients completing ten cycles compared with the TROPIC study (18% vs. 28%). Nevertheless, these data indicate that SAEs such as febrile neutropenia are relatively well controlled in a clinical setting in which physicians administer prophylactic G-CSF and other preventive medicine to patients who are at high risk for the development of SAEs.

In the cabazitaxel-treated arm of the TROPIC study five patients died of cardiac problems within 30 days of cabazitaxel treatment.[10] According to the investigators, none of these cardiac events were related to cabazitaxel. A subsequent study, which directly investigated the relationship between cabazitaxel use and cardiac disorders, concluded that cabazitaxel had no significant effect on the QTc interval in patients with advanced solid tumors.[18] It is generally thought that the increased number of mortal cardiac events in the cabazitaxel-treated group of the TROPIC study was not related to cabazitaxel. In the Dutch CUP, one patient had a myocardial infarction between cabazitaxel courses; grade 5 TEAEs did not occur in participating patients.

Collected efficacy parameters in our study were OS, TTPP, and PFS. Time to radiologic or clinical progression was not determined, because clinical progression was not reported in a standardized format, and radiologic assessments had been performed based on the physician's decision. In general, most physicians performed radiologic tests only when other tools to measure disease progression, such as PSA measurements and clinical assessments, were inconclusive.

Median OS was considerably lower in the Dutch CUP population compared with OS in the cabazitaxel-treated population of the TROPIC study (8.7 vs. 15.1 months). The median TTPP was lower as well: 2.8 vs. 6.4 months. In the German CUP, the mean biochemical PFS and OS were 3.8 and 13.9 months, respectively. This was comparable to our results, in which the mean TTPP and OS were 3.8 and 12.9 months, respectively. Our results were also similar to preliminary results from the Spanish EAP; the median PFS in this study was 4.4 months.[17] The Italian CUP did not report efficacy data. The most likely explanation for this discrepancy between the TROPIC study and our study is a difference in the patient population: in general, patients in the Dutch CUP had more advanced prostate cancer than patients in the TROPIC study. Only 31% of cabazitaxel-treated patients in the TROPIC study had received two or more chemotherapy regimens; in the Dutch CUP 49.0% of patients had received two or more chemotherapy regimens. Furthermore, ten patients (20.4%) had received abiraterone (five patients), enzalutamide (four patients) and/or immunotherapy (ipilimumab/CNTO95) (two patients) before cabazitaxel, whereas patients enrolled in the TROPIC study had no previous treatment with these agents. Recent research concludes that treating patients with abiraterone or enzalutamide before taxane therapy may reduce the efficacy of taxanes.[20, 21] In a retrospective study of 35 chemonaive patients treated with abiraterone who subsequently received docetaxel at progression, a median OS of 12.5 months and a PSA response in 9 patients (25.7%) were reported with docetaxel, which is significantly lower than figures reported in the TAX-327 trial (19.8 months and 45%, respectively).[3, 20] Another evident difference in the patient population is the number of metastatic sites in patients: 85.7% of patients in the Dutch CUP had ≥2 metastatic sites, whereas only 61% of patients in the TROPIC study had ≥2 metastatic sites.[10] Furthermore, patients in our study had a median PSA of 355.5 ng/ml at the start of cabazitaxel treatment, whereas the median PSA was 143.9

ng/ml in patients who would be treated with cabazitaxel at the start of the TROPIC study. These observations strengthen the need for observational studies as presented in this chapter: the current clinical situation does not necessarily comply with the study population of the phase III registration study.

Recently, hormonal therapy with abiraterone acetate has been approved by the US Food and Drug Administration (FDA) and in the Netherlands as a second-line therapy for patients with mCRPC, based on the results of the COU-AA-301 study.[22] Thus, both cabazitaxel and abiraterone acetate are therapeutic options for patients with symptomatic mCRPC who progressed during or after docetaxel treatment. Enzalutamide has just been approved by the US FDA as well but is awaiting approval in the European Union; a phase III study has indicated prolonged OS when administered as second-line therapy in patients with mCRPC.[23] CUPs with enzalutamide are ongoing. Finally, docetaxel could be re-introduced after an initial response and a substantial docetaxel-free interval. There is no scientific evidence for the most preferred treatment strategy in patients with symptomatic mCRPC after docetaxel-based therapy. Therefore, a wide variety of clinical studies is being performed to create a scientific basis for the optimal treatment strategy for this group of patients.

To further improve the tolerability of cabazitaxel in patients with mCRPC without compromising efficacy, three phase II studies are assessing different dosing schedules, such as weekly cabazitaxel at 10 mg/m^2 or biweekly cabazitaxel at 16 mg/m^2.[24-26] Furthermore, a phase III study (PROSELICA) is comparing the efficacy of 20 mg/m^2 cabazitaxel to 25 mg/m^2 cabazitaxel, both administered once every three weeks.[27, 28] The CABARESC study is a phase II study in which budesonide is added to cabazitaxel to prevent cabazitaxel-induced diarrhea, the most frequent grade ≥3 non-hematologic adverse event in the TROPIC study.[29] In another clinical study, octreotide is added to cabazitaxel to prevent diarrhea as well.[30] However, considering the low percentage of grade ≥3 diarrhea reported in this CUP and other CUPs, one can question whether these studies are still needed, because it seems that diarrhea is already well controlled in a regular clinical setting.

Therapy efficacy and/or tolerability may be further improved by combining cabazitaxel with other treatments, such as the combination of cabazitaxel with custirsen (OGX-011)[31], abiraterone acetate[32], tasquinimod[33], carboplatin[34], or bavituximab[35]. Other studies are investigating the use of cabazitaxel in patients with less advanced prostate cancer, such as the FIRSTANA study, which compares the efficacy of cabazitaxel (25 or 20 mg/m^2) to docetaxel as first-line therapy in patients with mCRPC.[36, 37] Further clinical benefit could be achieved by selecting a subgroup of patients with mCRPC that is most likely to respond to cabazitaxel. Since fourteen patients (28.6%) in the Dutch CUP did not respond to cabazitaxel treatment at all, and patients who initially responded exhibited a wide variation in the duration of response, a marker predicting cabazitaxel response would prevent unnecessary treatment of patients, thereby cutting costs, reducing adverse events, and preventing delays in initiating other therapies that are targeting the tumor. No such marker has been identified

yet. The initial Gleason score has been identified as a predictive factor in abiraterone-treated patients, an initial Gleason score of 8 to 10 resulting in a lesser response to the agents.[38] A short time (<12 months) between the time of prostate cancer and mCRPC diagnosis was a prognostic factor for a lower PFS in patients treated with abiraterone and other endocrine-manupilating agents.[39] Since PFS in docetaxel-treated patients was not associated with the time to castration resistance, this may be a predictive factor in abiraterone-treated patients as well. The time to castration-resistance and the initial Gleason score were not significantly predictive or prognostic for the cabazitaxel response (TTPP/OS) in the Dutch CUP.

Our study and other studies suggest that pretreatment with abiraterone or enzalutamide may compromise the efficacy of cabazitaxel.[20, 21] However, patients who received this pretreatment may have had more aggressive or more advanced prostate cancer. The ECOG performance status at the start of cabazitaxel treatment did not differ significantly though (p=0.294, data not shown). Abiraterone and enzalutamide are currently being assessed as first-line therapy in patients with mCRPC.[40, 41] Considering the results from our study and other studies,[20, 21] we think potential cross-resistance needs to be assessed more thoroughly in prospective randomized drug sequence studies.

The results of the Dutch CUP further suggest that if patients had received <10 docetaxel cycles, indicating they had disease progression or SAEs during docetaxel treatment, they are likely to have a lesser response to cabazitaxel treatment compared with patients who received ≥10 docetaxel cycles. This observation was not confounded by the number of cabazitaxel cycles received, because these numbers were similar between the two groups. Therefore, cabazitaxel may have a higher efficacy in patients who received at least 10 docetaxel treatments, suggesting that some patients are particularly sensitive to taxanes and reach a significant survival benefit with this therapy. In summary, the relationship between previous docetaxel, abiraterone, or enzalutamide treatment and cabazitaxel response needs further study, and more specific predictive markers need to be identified.

With the introduction of cabazitaxel as a second-line therapy in patients with mCRPC, treatment options for this group of patients have expanded. Results from the Dutch CUP study indicate that cabazitaxel has effect in patients with advanced mCRPC in a clinical setting, delaying disease progression and/or improving symptoms, while resulting in moderate toxicity. However, we are still at the beginning stage of the expansive research that is needed to optimize the treatment algorithm for patients with mCRPC.

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