Original Study

Cabazitaxel in Patients With Metastatic Castration-Resistant Prostate Cancer: Results of a Compassionate Use Program in The Netherlands

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Abstract

We present a safety and efficacy data analysis of cabazitaxel treatment in 49 patients with metastatic castrate-resistant prostate cancer (mCRPC) who participated in the Dutch Compassionate Use Program (CUP). Median time to prostate-specific antigen (PSA) progression was 2.8 months, median overall survival (OS) was 8.7 months. Toxicities were acceptable, the most frequent serious adverse events (SAEs) being hematuria (8.2%) and urosepsis (6.1%).

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. **Patients and Methods:** Safety and efficacy data of all 5 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%], 42 patients had ≥ 2 metastatic sites. Patients received on average 6 cabazitaxel cycles (range, 1-21). A dose reduction or dose delay occurred in 13 and 20 patients [26.5% and 40.9%] 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 (TEAEs). Serious adverse events (SAEs) occurred in 16 (32.7%) patients; the most frequent SAEs were hematuria (4 patients [8.3%]) and urosepsis (3 patients [6.3%]). 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.

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Introduction

Metastatic castrate-resistant prostate cancer (mCRPC) is the second deadliest cancer in men in the United States, 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 2 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; 5 of 6 mice had a tumor-free survival of $\geq$ 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-hour intravenous infusion once every 3 weeks, the dose-limiting toxicity being neutropenia.[8,9] Of the 8 patients with mCRPC who received cabazitaxel treatment at doses $\leq$ 25 mg/m^2 in the phase I study, 2 patients had an objective partial response for $\geq$ 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 hour 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; $P <$ .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 nonaggressive 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; $P <$ .0001), and the median time to PSA progression (TTPP) was increased from 3.1 to 6.4 months. However, both grade $\geq$ 3 hematologic and nonhematologic adverse events had an increased incidence in cabazitaxel-treated patients. The most frequent grade $\geq$ 3 hematologic adverse events were neutropenia and leukopenia, which occurred in 303 [82%] and 253 [68%] of all cabazitaxel-treated patients with mCRPC, respectively, vs. 215 [58%] and 157 [42%], respectively, in mitoxantrone-treated patients. Febrile neutropenia occurred in 28 cabazitaxel-treated patients [8%] and in 5 mitoxantrone-treated patients [1%]. The most frequent grade $\geq$ 3 nonhematologic adverse event was diarrhea, which occurred in 23 cabazitaxel-treated patients [6%] and in 1 mitoxantrone-treated patient [$<$ 1%]. In the TROPIC study, 9 mitoxantrone-treated patients [2.4%] died within 30 days of the last dose of the study drug (6 of disease progression), whereas in the cabazitaxel-treated group, 18 patients [4.9%] 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 United States 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 5 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 $\geq$ 18 years; have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; have a life expectancy of $\geq$ 3 months; and have adequate bone marrow, liver, and renal functions. Patients were excluded from participation if they had received previous radiotherapy to $\geq$ 40% of the bone marrow, previous radionuclide therapy, or anticancer therapy within 4 weeks of enrollment. Patients were also excluded when they presented with grade $\geq$ 2 peripheral neuropathy, grade $\geq$ 2 stomatitis, an infection treated with a 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, prednisone or prednisolone, 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 hour 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 guidelines, such as previous episodes of (febrile) neutropenia, age > 65 years, poor performance and/or nutritional status, extensive previous radiation ports, 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 antiemetic prophylaxis was administered at the physician's discretion. The recommended additional antiemetic prophylaxis was metoclopramide. Patients who experienced grade ≥ 3 nausea and/or vomiting received more aggressive antiemetic prophylaxis, namely, ondansetron. However, physicians were allowed to diverge from this protocol. Therefore, 4 patients received granisetron as antiemetic 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 ≤ 75,000/mm^3, grade ≥ 3 nonhematologic toxicities (except alopecia and nail changes) that had not recovered to baseline, an aspartate aminotransferase/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 2 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 antiemetic 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 reescalation or further dose reductions were not allowed.

Although cabazitaxel treatment was discontinued after a maximum of 10 cycles in the TROPIC study, physicians and patients were allowed to decide to continue treatment beyond 10 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, computed tomographic 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 (eg, computed tomography, magnetic resonance imaging, radiography, bone scanning, and electrocardiography) 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 3 weeks, whereas other diagnostic tests such as radiologic assessments were performed at the physicians' 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 at least 12 weeks of treatment. Furthermore, the patient's TTPP was not determined if a different treatment was started before PSA progression was measured or if more than 3 months elapsed between 2 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 decrease or increase 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 computed tomographic or bone scans, magnetic resonance images, or radiographs), 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, ie, 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] The PFS could therefore 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 patients did not have an improved condition overall. A partial response was defined as a PSA decrease of $\geq$ 50% compared with the baseline in at least 2 separate PSA measurements 3 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 1 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 (SPSS, Inc, Chicago, IL) 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 mCRPC 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 or 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 from 5 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 2 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 1 administration of cabazitaxel was 64.6 years (IQR, 58.6-70.0 years); 3 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 2 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 (5 [10.2%]), enzalutamide (4 [8.2%]), and/or immunotherapy (ipilimumab/CNTO95) (2 [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) (Figure 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 [40.9%] required a dose delay (Table 2).

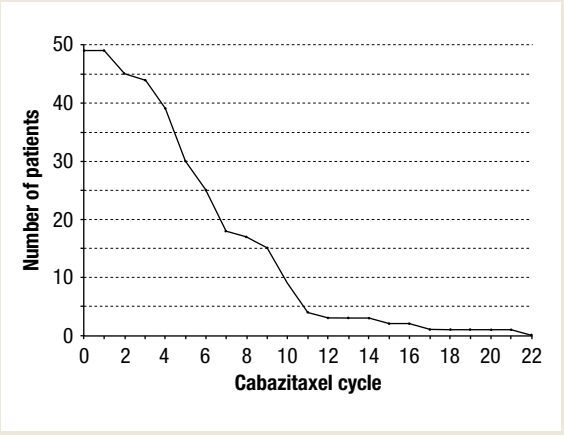
G-CSF was administered for prophylactic use to 8 patients [16.3%] for a total of 49 cycles. These 8 patients completed a median

Table 1 Baseline Characteristics of Patients Treated With Cabazitaxel Through the CUP (n = 49)

Age	
Mean (y [SD])	63.6 (8.1)
Median (y [IQR])	64.6 (58.6-70.0)
Patients < 65 y	26 (53.1%)
Patients ≥ 75 y	3 (6.1%)
Performance Status at Start of Therapy	
ECOG PS 0	2 (6.1%)
ECOG PS 1	35 (71.4%)
ECOG PS 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/m^2)	
Mean (SD)	742.50 (358.58)
Median (IQR)	750 (450-900)
Disease progression relative to docetaxel administration	
< 0 (during treatment)	9 (18.4%)
< 3 mo since last dose	17 (34.7%)
≥ 3-< 6 mo since last dose	12 (24.5%)
≥ 6 mo since last dose	11 (22.4%)
Median time from last docetaxel dose to disease	3.22 (1.36-6.87)
Progression (months [IQR])	
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 otherwise specified.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; mCRPC = metastatic castrate-resistant prostate cancer; PS = performance score; PSA = prostate-specific antigen; SD = standard deviation.

Figure 1 Cabazitaxel Treatment in the Dutch Compassionate Use Program (CUP) Population. The Graph Displays the Number of Patients Treated at Cycle *n*



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, 2 patients with docetaxel, and 3 patients with mitoxantrone. Three patients were treated with ipilimumab or placebo in a study setting, and 4 patients were treated with enzalutamide. Finally, 3 patients received a second cabazitaxel regimen after treatment with abiraterone acetate.

Safety

All patients reported TEAEs during treatment; 46 patients [93.9%] 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 patients [32.7%], none of these adverse events resulted in patient death. Grade ≥ 3 events occurred in 25 patients [51.0%]; grade 4 events occurred in 5 patients [10.2%]. Sixteen patients [32.7%] discontinued treatment because of TEAEs.

All grade ≥ 3 TEAEs and SAEs, as well as grade 1/2 events that occurred in at least 2 patients, are listed in Table 3. The most frequent TEAE was fatigue, which occurred in 30 patients [61.2%];

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 who completed ≥ 10 cycles	9 (18.4%)
Treatment time (d)	
Mean (SD)	144 (88)
Median (range)	126 (21-469)
Number of Patients With Treatment Delay	20 (40.9%)
Number of Patients With Dose Reduction	13 (26.5%)
Dose reduction ≤ cycle 10	12 (24.5%)

Data are number of patients (%) unless specified otherwise.
Abbreviation: SD = standard deviation.

grade ≥ 3 fatigue occurred in 5 patients [10.2%]. Other nonhematologic grade ≥ 3 TEAEs that were reported in at least 2 patients were urosepsis (3 patients [6.1%]), bone pain (3 patients [6.1%]), paraplegia (2 patients [4.1%]), pulmonary embolism (2 patients [4.1%]), urinary tract infections (2 patients [4.1%]), and a decreased appetite (2 patients [4.1%]). The most frequent reported nonhematologic 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 × 8 Gy and 4 × 5 Gy) to the pelvic region before cabazitaxel therapy. Two patients with grade 2 hematuria (out of 4 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 1 patient. Other frequently reported nonhematologic adverse events (all grades) were nausea (22 patients [44.9%]), diarrhea (20 patients [40.8%]), vomiting (13 patients [26.5%]), and malaise (10 patients [20.4%]) (Table 3). Grade 1 or 2 peripheral neuropathy was reported in 9 patients [18.4%]. Eleven patients [22.4%] had a weight loss of ≥ 5% of their total body weight.

Hematologic adverse events occurred in 17 patients [34.7%]. Of all cabazitaxel-treated patients with mCRPC, 6 [12.2%] experienced grade ≥ 3 hematologic adverse events, of which grade ≥ 3 (febrile) neutropenia and anemia were the most frequent (2 patients [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) (Figure 2A, Table 4). Fourteen patients [28.6%] had continuous progressive disease despite cabazitaxel treatment; 9 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 (Figure 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 2 patients with the longest TTPP (13.3 and 10.5 months, respectively) had received the most cabazitaxel cycles (21 and 14, respectively). The 2 patients, in whom cabazitaxel treatment was discontinued after 10 cycles solely because of completion of 10 cycles, similar to the TROPIC study protocol, had a TTPP of 9.0 and 7.5 months, respectively. This suggests that it might be clinically beneficial to continue treatment beyond 10 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. 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 with mCRPC (Table 4). However, patients with a PSA < 500 ng/mL at the start of treatment had a longer OS than did patients with an initial PSA level of ≥ 500 ng/mL (10.1 vs. 7.9 months; $P = .016$). 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 at least 10 docetaxel cycles ($P = .049$ and $P = .015$, respectively) (Table 4). Furthermore, 10 of 12 patients [83.3%] who had a TTPP > 4 months had received ≥ 10 cycles of docetaxel before cabazitaxel treatment, whereas 4 of the 9 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 at least 10 docetaxel cycles, because the median number of cabazitaxel cycles was 5 and 6, respectively ($P = .163$) (Supplementary Table 1). Similarly, the percentage of patients who discontinued treatment because of adverse events did not differ between the 2 groups (30.0% and 27.6%, respectively; $P = .858$). Patients pretreated with abiraterone and/or enzalutamide had a decreased OS (5.9 vs. 10.0 months; $P = .027$) (Table 4). The median TTPP tended to differ significantly as well (2.1 vs. 3.2 months; $P = .052$). Between these groups of patients, the median number of cabazitaxel cycles was not significantly different (4 vs. 6; $P = .065$) (Supplementary Table 1).

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 2 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 afterward. Six patients had an initial PSA decrease but had their serum PSA levels increase to the baseline PSA level or higher during the first

Table 3 Adverse Events Reported During Cabazitaxel Treatment

Patients With Possibly Related TEAEs	46 (93.9%)
Patients who discontinued treatment due to TEAEs	16 (32.7%)
Patients with hematologic 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 3/4		SAE		All Grades	
Any Adverse Event	25	(51.0%)	16	(32.7%)	49	(100%)
Hematologic 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%)
Nonhematologic 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%)

Table 3 (continued)

	Grade 3/4		SAE		All Grades	
Rectal hemorrhage	0	—	0	—	3	(6.1%)
Dysgeusia	0	—	0	—	3	(6.1%)
Peripheral sensory neuropathy	0	—	0	—	3	(6.1%)
Peripheral edema	0	—	0	—	3	(6.1%)
Abnormal hepatic function	0	—	0	—	2	(4.1%)
Nasopharyngitis	0	—	0	—	2	(4.1%)
Dyspnea	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, version 3.0. All adverse events that occurred in at least 2 patients are listed, as well as all grade 3/4 adverse events and SAEs.
Abbreviations: SAE = serious adverse event; TEAEs = treatment-emergent adverse events.

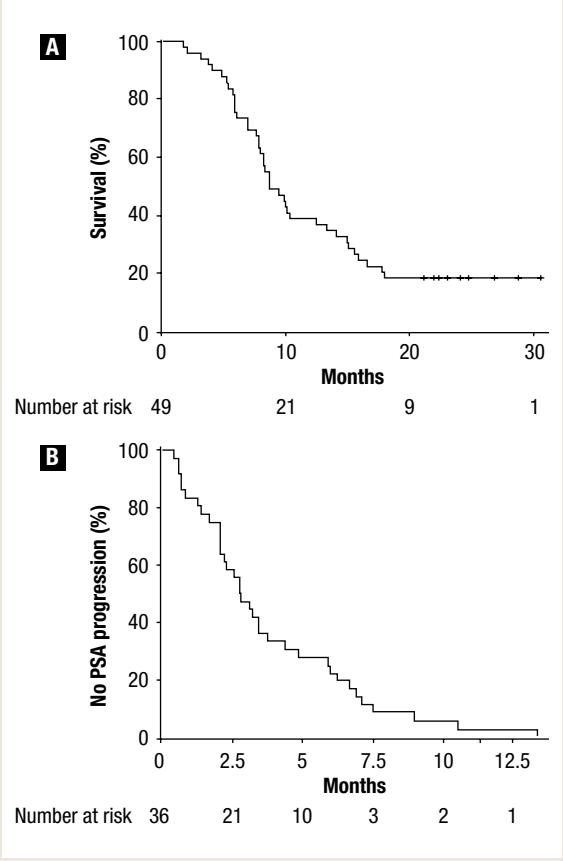
4 cycles. The remaining 27 patients had a decrease in PSA levels that was sustained during the first 4 cycles of cabazitaxel treatment. Of these patients, 19 had a PSA decrease of ≥ 25% for at least 4 cycles. The maximum decrease in PSA was 92.9%; this patient's PSA level decreased from 3669 to 172.4 ng/mL during 6 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 (Supplementary Table 2). Patients who had at least a 25% decrease in PSA after 4 cycles of cabazitaxel had a median TTPP and OS of 6.2 months (IQR, 4.4-7.5 months) and 16.6 months (9.4-undetermined months), respectively, compared with 2.1 months (0.8- 2.8 months) and 7.9 months (IQR, 5.9-10.0 months) in the rest of the patients ($P < .001$). Patients who had at least a 50% decrease in PSA had a median TTPP and OS of 6.9 months (IQR, 5.9-9.0 months) and 16.6 months (15.0-undetermined months), respectively, compared with 2.3 months (1.4-3.5 months) and 8.3 months (IQR, 5.9-13.3 months) in the rest of the patients ($P = .017$ and $P = .024$, 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 ($P = .854$ and $P = .644$, 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 nonhematologic 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 47.9% 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 in 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 with mCRPC, 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 3 studies assessed adverse events once every 3 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 partially result from the use of prophylactic G-CSF in high-risk patients according to American Society of Clinical Oncology 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 3 weeks, simulating the clinical practice setting.[3] Most of the TEAEs that were

Figure 2 Kaplan-Meier Estimates of (A) Overall Survival (OS) and (B) Time to PSA Progression (TTPP) in the Cabazitaxel-Treated Compassionate Use Program (CUP) Population. Vertical Bars on the Curves in A Display Censored Observations



missed by doing an assessment every 3 weeks instead of weekly were asymptomatic TEAEs that disappeared within 3 weeks (such as neutropenia without fever) and were therefore 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 10 cycles compared with the TROPIC study (19% 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, 5 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, 1 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 did patients in the TROPIC study. Although only 31% of cabazitaxel-treated patients in the TROPIC study had received 2 or more chemotherapy regimens, in the Dutch CUP 49% of patients had received 2 or more chemotherapy regimens. Furthermore, 10 patients [20.4%] had received abiraterone, enzalutamide, and/or immunotherapy (ipilimumab/CNTO95) 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 TAX327 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 with mCRPC 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 article: 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 progress during or after docetaxel treatment. Enzalutamide has just been approved by the US FDA as

Table 4 Efficacy Parameters of Cabazitaxel Treatment

OS (n = 49)	
Mean (mo [95% CI])	12.9 (10.3-15.5)
Median (mo [IQR])	8.7 (6.0-15.9)
TTPP (n = 36)	
Mean (mo [95% CI])	3.8 (2.8-4.8)
Median (mo [IQR])	2.8 (1.7-5.9)
PFS (n = 46)	
Mean (mo [95% CI])	3.8 (2.8-4.7)
Median (mo [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 (mo [95% CI])	15.6 (12.5-18.8)
Median (mo [IQR])	13.3 (7.9-undetermined)

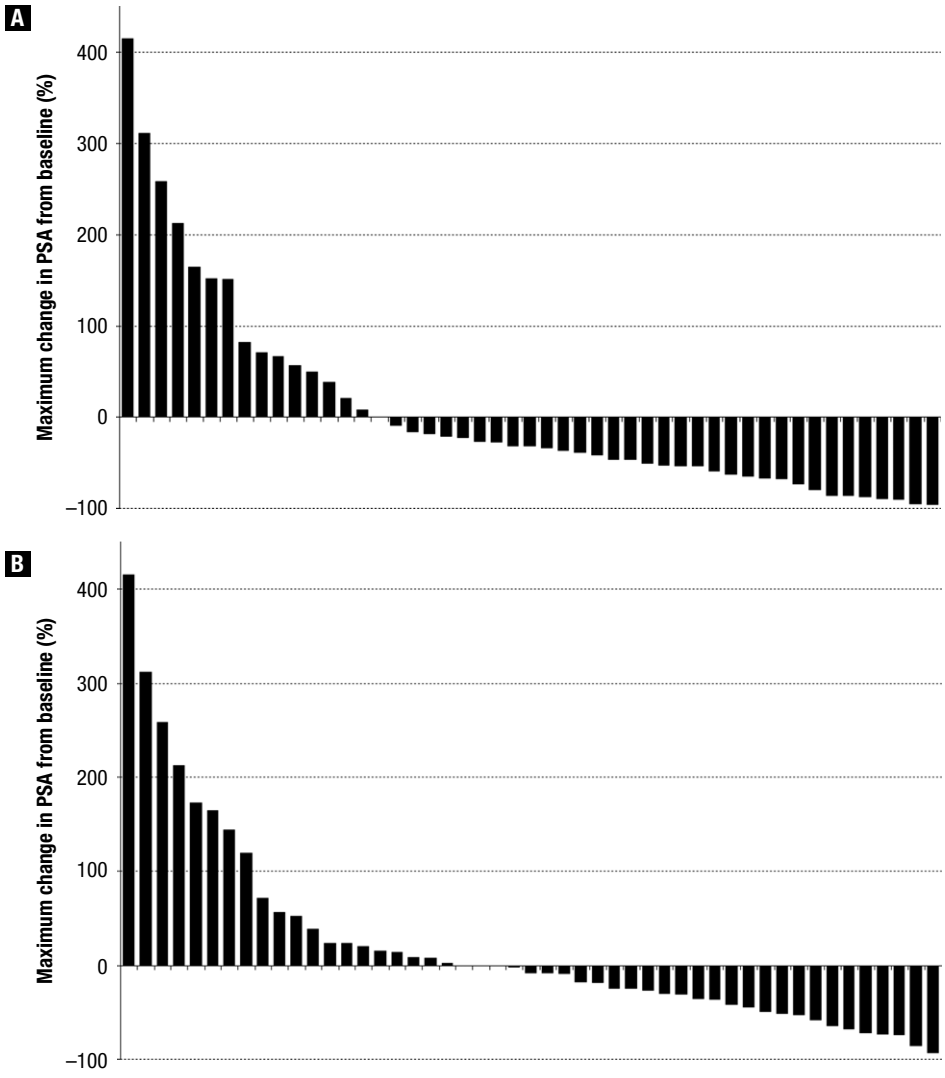
Patient Characteristic	TTPP			OS		
	Number of Patients	Median (IQR)	*P* Value	Number of Patients	Median (IQR)	*P* Value
Age < 65 y	20	3.2 (1.4-4.9)	.458	26	8.3 (5.9-17.8)	.731
Age ≥ 65 y	16	2.6 (2.1-5.9)		23	9.9 (7.6-15.9)	
BMI < 25	10	2.8 (2.1-4.9)	.972	15	9.9 (6.9-undetermined)	.616
BMI 25-30	20	2.6 (1.4-4.9)		24	8.2 (5.7-14.9)	
BMI > 30	5	3.5 (2.1-4.4)		9	13.3 (8.7-15.9)	
Time to mCRPC < 12 mo	8	2.1 (0.7-0.1)	.282	11	7.6 (5.9-10.1)	.121
Time to mCRPC ≥ 12 mo	28	2.8 (2.1-6.0)		38	9.9 (6.0-17.8)	
Gleason Score < 8	10	2.8 (2.2-3.5)	.407	12	12.5 (6.0-15.6)	.750
Gleason Score 8-10	16	2.5 (2.1-6.7)		22	9.4 (8.2-17.9)	
ECOG PS < 2	28	2.8 (2.1-6.0)	.118	37	10.0 (7.6-16.6)	.347
ECOG PS ≥ 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)	.655	26	10.1 (7.9-undetermined)	.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)	.049	19	7.8 (5.9-10.3)	.015
Docetaxel ≥10 Cycles	21	3.5 (2.1-6.9)		30	10.0 (7.9-undetermined)	
Previous Treatment With Abiraterone/Enzalutamide	7	2.1 (1.3-3.1)	.052	8	5.9 (5.4-8.3)	.027
No Previous 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 in this subgroup at the cutoff date.
Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance score; IQR = interquartile range; mCRPC = metastatic castrate-resistant prostate cancer; PSA = prostate-specific antigen; TTPP = time to PSA progression.

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 reintroduced after an initial response and a substantial docetaxel-free interval. There is no scientific evidence for the most preferred treatment strategy in symptomatic patients with mCRPC after docetaxel-based therapy. A wide variety of clinical studies is therefore 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, 3 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] Further-

Figure 3 Waterfall Plots Showing (A) the Maximal Change in Serum Prostate-Specific Antigen (PSA) Levels From Baseline During or After Cabazitaxel Therapy Before Initiation of Another mCRPC Treatment and (B) the Change in Serum PSA Levels From Baseline After 4 Cycles of Cabazitaxel. If Patients had Been Treated for < 4 Cycles, the Serum PSA Level During or After the Last Cabazitaxel Cycle was Used



more, 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 3 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 nonhematologic 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 14 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 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-manipulating 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 ($P = .294$, 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 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 2 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.

Conclusion

This study reports the safety and efficacy of cabazitaxel use in all 49 patients with mCRPC treated in the CUP in the Netherlands. In our study population, cabazitaxel was generally well tolerated: Grade ≥ 3 adverse events were observed in 23 patients [51.0%]. Grade ≥ 3 hematologic adverse events occurred in 6 patients [12.2%]; 2 patients [4.2%] experienced febrile neutropenia. Most likely, neutropenic adverse events were relatively low because of the addition of prophylactic G-CSF for patients at risk and by monitoring adverse events once every 3 weeks instead of weekly. The most frequent SAEs were hematuria (4 patients [8.2%]) and urosepsis (3 patients [6.1%]). Additional frequent grade ≥ 3 adverse events were fatigue and bone pain, which occurred in 5 [10.2%] and 3 [6.1%] of patients, respectively. Grade ≥ 3 cardiac events and diarrhea each occurred in 1 patient. No patient experienced grade ≥ 3 neuropathy. Importantly, no death was possibly related to cabazitaxel treatment. These results imply that in clinical practice, cabazitaxel is well tolerated in patients with mCRPC. The number of patients with SAEs (16 patients [32.7%]) was lower than expected, most likely because physicians closely monitored adverse events and adjusted treatment accordingly, eg, by a dose delay. Additional studies need to be performed to assess and decrease adverse events by reporting adverse events observed in other CUPs in Europe, by changing the dosing regimen, and by addition of medicines to prevent SAEs.

Median follow-up was 24.1 months (IQR, 22.4-26.9 months). Median OS was 8.7 months (IQR, 6.0-15.9 months); based on PSA values, median TTPP was 2.8 months (IQR, 1.7-5.9 months) and median PFS was 2.8 months (IQR, 1.7-4.9 months). A partial response was seen in 9 patients [18.4%]. Because 14 patients [28.6%] had continuous disease progression during cabazitaxel treatment, it is important to identify markers that predict cabazitaxel response. Our study indicates that patients who responded well to docetaxel treatment had a better response to cabazitaxel treatment. Additional research needs to be performed regarding this marker and other potential predictive and prognostic markers. In line with other studies, we conclude that patients who received abiraterone and/or enzalutamide before cabazitaxel treatment had a lesser response to cabazitaxel. More studies are needed to study the cross-resistance to taxane treatment after abiraterone or enzalutamide therapy. Furthermore, currently there is ongoing research to improve the efficacy of cabazitaxel by changing the dosing regimen and by combining cabazitaxel with other therapy options. Finally, investigations are needed to determine whether administration of cabazitaxel at an earlier stage of prostate cancer has clinical advantage as well, eg, as first-line therapy in patients with mCRPC.

Clinical Practice Points

- Results from the TROPIC study resulted in the approval of cabazitaxel for use as second-line therapy for patients with mCRPC. Cabazitaxel increased median survival (OS) and PFS significantly compared with mitoxantrone treatment. However, toxicity was higher in the cabazitaxel-treated group.
- In the Dutch CUP, 49 patients with mCRPC received cabazitaxel in a routine clinical practice setting. Toxicities were acceptable in this program. No patient had a grade 5 event. The most frequent SAEs reported were hematuria (4 patients [8.2%]) and urosepsis (3 patients [6.1%]). Febrile neutropenia occurred in 2 patients [4.1%].
- Median OS in the CUP was 8.7 months compared with 15.1 months in the TROPIC study. Of note, patients in the CUP had more advanced prostate cancer. Nevertheless, disease control was reached in 35 patients [71.4%], and 9 patients [18.4%] had a partial response. The efficacy of cabazitaxel was decreased in patients pretreated with abiraterone and/or enzalutamide (8 patients

[16.3%]) and patients who completed < 10 cycles of docetaxel cabazitaxel.

- As multiple novel therapies for mCRPC are approved by the US FDA or are in advanced stages of clinical research (cabazitaxel, abiraterone acetate, enzalutamide, tasquinimod), it is important to study these compounds extensively to come to an evidence-based conclusion for the preferred treatment strategy for patients with mCRPC. This study indicates that cabazitaxel is well tolerated and effective in patients with mCRPC in a routine clinical setting. However, it is important to search for predictive markers for cabazitaxel response and study the optimal treatment sequence in more detail.

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Disclosure

Dr Van Oort, Dr Gerritsen, and Dr Coenen are members of the advisory board of cabazitaxel, Sanofi-Aventis. All other authors have stated that they have no conflicts of interest.

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Supplementary Table 1 Treatment Characteristics of Subgroups of Patients

	Number of Patients	Median Cabazitaxel Cycles (IQR)		Number of Patients Who Discontinued Due to AE (%)
Docetaxel <10 Cycles	20	5 (3-6)	p = 0.163	6 (30.0%)
Docetaxel ≥10 Cycles	29	6 (4-9)		8 (27.6%)
Abiraterone/Enzalutamide Pretreatment	8	4 (4-5)	p = 0.065	3 (37.5%)
No Abiraterone/Enzalutamide Pretreatment	41	6 (4-9)		11 (26.8%)

IQR = interquartile range; AE = adverse event.

Supplementary Table 2 Time to PSA Progression (TTPP) and Overall Survival (OS) in Cabazitaxel-Treated mCRPC Patients Based on the PSA Response After 4 cycles

	TTPP			OS		
	Number of Patients	Median (IQR)		Number of Patients	Median (IQR)	
PSA decrease ≥25%	14	6.2 (4.4-7.5)	p < 0.001	19	16.6 (9.4-undetermined)	p < 0.001
No PSA decrease ≥25%	22	2.1 (0.8-2.8)		30	7.9 (5.9-10.0)	
PSA decrease ≥50%	7	6.9 (5.9-9.0)	p = 0.017	10	16.6 (15.0-undetermined)	p = 0.024
No PSA decrease ≥50%	29	2.3 (1.4-3.5)		39	8.3 (5.9-13.3)	
PSA decrease 25-50%	7	6.2 (3.2-7.5)	p = 0.854	9	14.9 (9.4-undetermined)	p = 0.644
PSA decrease >50%	7	6.9 (5.9-9.0)		10	16.6 (15.0-undetermined)	

The IQR could not be determined if >25% of patients were alive in this sub-group at the cutoff date.
PSA = prostate-specific antigen; IQR = interquartile range.