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Original Study

Second-Line Cabazitaxel Treatment in Castration-Resistant Prostate Cancer Clinical Trials Compared to Standard of Care in CAPRI: Observational Study in the Netherlands

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Abstract

In the Dutch CAPRI registry, cabazitaxel treatment as the standard of care and in trials was analyzed. Patients treated with cabazitaxel in trials were fitter and showed outcomes comparable to registration trials. Conversely, those treated in daily practice showed features of more aggressive disease and worse outcome. This may be explained by a worse prognosis at cabazitaxel initiation.

Background: Cabazitaxel has been shown to improve overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients after docetaxel in the TROPIC trial. However, trial populations may not reflect the real-world population. We compared patient characteristics and outcomes of cabazitaxel within and outside trials (standard of care, SOC). **Patients and Methods:** mCRPC patients treated with cabazitaxel directly after docetaxel therapy before 2017 were retrospectively identified and followed to 2018. Patients were grouped on the basis of treatment within a trial or SOC. Outcomes included OS and prostate-specific antigen (PSA) response. **Results:** From 3616 patients in the CAPRI registry, we identified 356 patients treated with cabazitaxel, with 173 patients treated in the second line. Trial patients had favorable prognostic factors: fewer symptoms, less visceral disease, lower lactate dehydrogenase, higher hemoglobin, more docetaxel cycles, and longer treatment-free interval since docetaxel therapy. PSA response ($\geq$ 50% decline) was 28 versus 12%, respectively ($P = .209$). Median OS was 13.6 versus 9.6 months for trial and SOC

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subgroups, respectively (hazard ratio = 0.73, $P = .067$). After correction for prognostic factors, there was no difference in survival (hazard ratio = 1.00, $P = .999$). Longer duration of androgen deprivation therapy treatment, lower lactate dehydrogenase, and lower PSA were associated with longer OS; visceral disease had a trend for shorter OS. **Conclusion:** Patients treated with cabazitaxel in trials were fitter and showed outcomes comparable to registration trials. Conversely, those treated in daily practice showed features of more aggressive disease and worse outcome. This underlines the importance of adequate estimation of trial eligibility and health status of mCRPC patients in daily practice to ensure optimal outcomes.

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Keywords: Postdocetaxel, Real-world outcomes, Registry, Trial eligibility, Trial population

Introduction

The combination of docetaxel plus prednisone remains a recommended first-line therapy for symptomatic metastatic castration-resistant prostate cancer (mCRPC) patients who are fit to receive chemotherapy.[1,2] In patients who experienced disease progression during or after treatment with docetaxel plus prednisone, the efficacy of cabazitaxel plus prednisone was superior to mitoxantrone plus prednisone in terms of overall survival (OS), as shown in the TROPIC trial.[3] In a comparable population, abiraterone plus prednisone, enzalutamide, and radium-223 were shown to improve OS to a similar extent compared to placebo.[4-6] Results of prospective randomized trials on treatment sequences in postdocetaxel patients are lacking. Moreover, retrospective series fail to show clear hints for optimal sequencing.[7] This led to the situation that decisions on postdocetaxel treatment are made by clinicians and patients without high-level evidence informing the decision.

The benefits established in efficacy trials can frequently not be demonstrated in clinical practice at the community level.[8] The clinical effectiveness of cabazitaxel is less well known. Median OS (mOS) in retrospective studies is shorter than in the interventional TROPIC, PROSELICA, and AFFINITY trials (real-world mOS of 7.0-12.7 months vs. trial mOS of 13.4-15.1 months, respectively).[3,9-13] However, subgroups of patients treated with an extra life-prolonging drug (LPD) in third-line (postcabazitaxel) therapy do better with mOS, reaching 18.2 to 22.7 months.[11,14-16]

Patients in clinical trials are typically selected according to strict eligibility criteria, with the aim to include a homogeneous and fit population.[17] Furthermore, clinical trial recruitment tends to concentrate in selected hospitals with an experienced clinical research team. Trial protocols optimize baseline monitoring, treatment evaluation, and treatment compliance. Real-world treatment lacks eligibility criteria and is provided in all hospitals, regardless of clinical trial experience. Real-world patients differ from trial patients and typically include older patients and patients with more comorbidities.[18] Real-world practice may also be variable in differential monitoring, compliance, (budget) constraints, and increased treatment options over time.[17] We have shown that patients who are treated in trials during the course of CRPC differ from patients who are treated outside the context of a clinical trial with respect to baseline prognostic variables at CRPC diagnosis, treatment, and outcomes.[18] Previous single-center reports have shown differences in clinical trial and real-world populations[19] as well as differential outcomes for docetaxel treatment in CRPC.[19,20]

In daily practice, it is challenging to optimize treatment efficacy by selecting the right patient for the right treatment in the right sequence. Moreover, it is challenging to extrapolate trial eligibility and results to a real-world population. The objective of this study was to compare patient characteristics, treatment, and outcomes of patients treated with cabazitaxel in second-line therapy, both in clinical trials and outside clinical trials (standard of care, SOC) in our multicenter observational CAPRI registry.

Patients and Methods

The study design, setting, participants, follow-up, and data collection of the CAPRI registry have been described in detail elsewhere.[18] In short, CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated observational multicenter cohort study in 20 hospitals in the Netherlands. Data collection started after approval by the local medical ethics committee and hospital board. Patients were retrospectively included from January 1, 2010, and data have been regularly updated for all patients from 2013 to 2018. The study population was an estimated 20% sample of all CRPC patients in the Netherlands in the study period. The study was registered in the Dutch Trial Registry as NTR3591.

Objective

Our objective was to assess the differences in patient characteristics, number of treatment cycles, prostate-specific antigen (PSA) response, and OS of patients treated with cabazitaxel in second-line mCRPC, defined as therapy provided directly after docetaxel regardless of predocetaxel treatment, both in clinical trials and outside clinical trials (SOC).

Participants

CRPC patients from the CAPRI registry diagnosed before January 1, 2016, and treated with docetaxel for mCRPC, followed by second-line cabazitaxel before January 1, 2017, were included in our analysis. If a patient was enrolled onto a clinical trial with cabazitaxel during the follow-up period, the patient was assigned to the trial subgroup; otherwise, the patient was assigned to the SOC subgroup. Patients not treated with docetaxel for CRPC were excluded.

Follow-up and Data Collection

Database cutoff was set on December 31, 2017.

Prognostic parameters were retrospectively registered by trained data managers and included age, Charlson comorbidity index, Gleason sum score, time receiving androgen deprivation therapy

Table 1 Baseline Characteristics at Initiation of Cabazitaxel Therapy

Characteristic	Cabazitaxel, Second Line (N = 173)			TROPIC
	SOC (N = 109)	Trial (N = 64)	*P*	Cabazitaxel Arm (N = 378)
Age (Y)				
Median (IQR)	68 (64-72)	67 (64-72)	.502	68 (62-73)
≥75 y (%)	17	13		18
Charlson Comorbidity Index (%)			0.112	NR
6	63	75		
7-8	32	25		
9-10	4	0		
>10	1	0		
Gleason Score (%)			.149	NR
≤7	29	38		
8-10	66	52		
Unknown	5	11		
Time to Response to ADT (Mos)			.780	NR
Median (IQR)	11 (7-16)	11 (6-23)		
Time on ADT (Mos)			.091	NR
Median (IQR)	25 (18-37)	30 (19-45)		
ALP (U/L)			.799	NR
Median (IQR)	222 (100-360)	192 (97-366)		
Missing (%)	18	11		
PSA (μg/L)			.711	
Median (IQR)	200 (65-567)	209 (79-500)		144
Missing (%)	12	8		1
Hemoglobin (mmol/L)			.029*	NR
Median (IQR)	7.1 (6.3-7.8)	7.7 (6.7-8.1)		
Missing (%)	17	11		
LDH (U/L)			.010*	NR
Median (IQR)	328 (252-504)	268 (209-397)		
Missing (%)	26	14		
ECOG Performance (%)			.186	
0	16	23		ECOG 0-1: 93%
1	49	56		
>1	9	3		NR
Missing	27	17		NR
Visceral Disease (%)			.038*	
No	29	45		NR
Yes	19	11		25%
Missing	52	44		NR
Opioid Use (%)			.140	NR
No	23	41		
Yes	28	27		
Missing	50	33		
Symptoms (%)			.033*	NR
No	6	17		
Yes	78	72		
Missing	16	11		

Baseline period defined as 42 days before to 7 days after start of cabazitaxel therapy. Total percentages may not equal 100 because of rounding.
Abbreviations: ADT = androgen deprivation therapy; ALP = alkaline phosphatase; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; NR = not reported; PSA = prostate specific antigen; SOC = standard of care.
*Statistically significant.

Table 2 Treatment Characteristics Before Docetaxel and After Cabazitaxel Therapy

Characteristic	Cabazitaxel Second Line (N = 173)			TROPIC
	SOC (n = 109)	Trial (n = 64)	*P*	Cabazitaxel Arm (N = 378)
Predocetaxel Therapy (%)				NR
Abiraterone	10	2	.099	
Enzalutamide	9	3	.131	
Radium-223	3	0	.181	
Antiandrogen	38	47	.232	
Estramustine	0	2	.191	
Ketoconazole	1	0	.442	
Prednisone	1	0	.442	
Study drug	3	11	.026*	
No. of Docetaxel Cycles				NR
Median (IQR)	7 (5-10)	10 (7-10)	.002*	
Missing (%)	1	3		
Time Since Last DOC Dose to Progression While Receiving DOC (Mos)			.097	
Median (IQR)	1.2 (0.6-3.6)	2.3 (0.9-4.6)		0.8 (0.0-3.1)
<1 month (valid %)	48	33		
Missing (%)	8	9		
Time Since Last DOC Dose (Mos)			.001*	NR
Median (IQR)	2.2 (0.9-4.7)	3.9 (2.0-6.0)		
<6 months (valid %)	86	74		
Missing (%)	5	5		
Type of Progression While Receiving DOC (%)				NR
PSA	84	91	.095	
Missing	6	6		
Radiologic	37	44	.761	
Missing	53	42		
Clinical	58	53	.704	
Missing	16	19		
Postcabazitaxel Therapy (%)				
Docetaxel	2	5	.280	10
Mitoxantrone	1	0	.442	30
Abiraterone	34	55	.005*	—
Enzalutamide	32	22	.295	—
Radium-223	11	11	.920	—
PSMA ligand	2	0	.552	—
Study drug	1	16	<.001*	—
No treatment	35	27	.258	NR
Total LPD Treatment Duration (Days), Median (IQR)			.156	NR
ART	185 (113-273)	152 (91-253)		
Taxane	218 (134-305)	268 (217-357)		
Radium	102 (52-148)	143 (72-217)		
Total	328 (221-508)	365 (269-534)		
No. of LPD Treatments (%)			.672	NR
2	26	27		
3	48	56		
>3	27	19		
Median (IQR)	3 (2-4)	3 (2-3)		
Range	2-6	2-6		

Table 2 Continued

Characteristic	Cabazitaxel Second Line (N = 173)			TROPIC
	SOC (n = 109)	Trial (n = 64)	*P*	Cabazitaxel Arm (N = 378)
No. of Treatments (Total)			.217	NR
Median (IQR)	3 (3-4)	4 (3-5)		
Range	2-8	2-7		

LPD treatments included docetaxel, abiraterone, cabazitaxel, enzalutamide, and radium-223.
Abbreviations: ART = antiretroviral therapy; DOC = docetaxel; IQR = interquartile range; LPD = life-prolonging drug; NR = not reported; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SOC = standard of care.
*Statistically significant.

(ADT), alkaline phosphatase, lactate dehydrogenase (LDH), prostate specific antigen (PSA), hemoglobin, Eastern Cooperative Oncology Group performance status, presence of visceral disease, opioid use, and symptoms. Time of response to ADT was defined as the time from start of ADT to diagnosis of CRPC.

Serious adverse events included hospital admissions and death within 30 days of last cabazitaxel administration.

Statistical Analysis

The sample size was not based on power calculations. Descriptive statistics were used. Differences in subgroups were tested for significance by either the chi-square test (categorical variables) or the Mann-Whitney *U* test (continuous variables). OS from start of cabazitaxel treatment to database cutoff was analyzed by Kaplan-Meier methods and Cox regression analyses. Differences were considered statistically significant at $P \leq .05$.

For PSA response, we report the maximum decline from baseline, and in case no decline occurred, we report the response at 12 weeks (ie, conforming to Prostate Cancer Clinical Trials Working Group 3 [PCWG3] guidelines[21]) or at last cycle (if treatment duration < 12 weeks). In our analysis, PSA response was unconfirmed, in contrast with PCWG3 guidelines. Patients with a PSA increase within 12 weeks without subsequent decrease were excluded from response analysis. Dose reduction was defined as a reduction of 20% or more; dose delay was defined as > 25 days between subsequent cycles. Severe adverse events only included hospital admissions (regardless of reason of admission) and deaths (regardless of cause of death) before 30 days after the last cabazitaxel infusion.

For imputation of missing baseline characteristics, multiple imputation by Monte Carlo Markov chain method was used. For statistical analyses, SPSS Statistics 22 (IBM, Armonk, NY) was used.

Results

Population

We identified 406 patients treated with cabazitaxel after docetaxel in the study period; 2 patients were excluded because docetaxel was provided for hormone-sensitive disease and not mCRPC. A total of 173 patients were treated with cabazitaxel in the second line (ie, after docetaxel). Of these 173 patients, 64 (37%) were treated within a trial (46, 11, 6, and 1 patients in the CABARESC, PROSELICA, Re-Cab, and CABENZA trials, respectively). A total of 184 of 406 patients received cabazitaxel in the third line (SOC n = 141, trial n = 43), and 47 patients received cabazitaxel in the fourth line or higher (SOC n = 45, trial n = 2) and were excluded from this analysis.

Median follow-up was 9.9 months (interquartile range, 5.2-18.0 months). A total of 149 patients (86%) had died at database cutoff. Baseline characteristics and treatment for CRPC are summarized in Tables 1 and 2. Patients treated in trials had a more favorable prognostic profile compared to SOC patients (significantly higher hemoglobin, lower LDH, less visceral metastases and fewer symptoms, and a trend for longer time receiving ADT). Trial patients also received more docetaxel cycles and had a longer interval between last docetaxel dose and start of cabazitaxel. Cabazitaxel trial patients participated significantly more often in other clinical trials than SOC patients. Subsequent treatment after cabazitaxel included significantly more abiraterone in trial patients (55% vs. 34%), whereas treatment with enzalutamide (22% vs. 32%), radium-223 (11% vs. 11%), and best supportive care (27% vs. 35%) was not significantly different.

The number of total treatment lines was not significantly different in trial patients and SOC patients (4 vs. 3, $P = .217$), and the total LPD treatment duration expressed as the sum of all LPD treatment durations in days was 365 versus 328 days ($P = .156$). LPD treatment with predocetaxel was infrequent.

Treatment Outcomes

Treatment intensity of cabazitaxel was numerically higher in trials compared to SOC, expressed by median number of cabazitaxel cycles (5 vs. 4, respectively; $P = .051$), proportion of patients reaching 10 therapy cycles (24 vs. 14%, respectively), and cumulative dose (228 vs. 165 mg; $P = .026$) (Table 3).

Serious adverse events (hospitalization and death) did not differ significantly between trial and SOC patients (Table 3). In the trial patients, dose adjustments were better documented (missing data, 9% vs. 31% in SOC patients). However, dose reduction or dose delay did not significantly differ between the groups.

In trial and SOC patients, PSA response (≥ 50% decline) was 28% versus 12% ($P = .209$). In patients receiving cabazitaxel directly after docetaxel, mOS was 13.6 and 9.6 months for trial patients and SOC, respectively (hazard ratio = 0.732; 95% confidence interval, 0.524-1.022; $P = .067$) (Table 4, Figure 1). The patients who were treated with at least an additional LPD after cabazitaxel therapy had a mOS from the first cabazitaxel treatment of 15.1 months, versus 4.6 months for patients who only received best supportive care after cabazitaxel treatment.

Table 3 Treatment Characteristics of Cabazitaxel Treatment

Characteristic	Cabazitaxel Second Line (N = 173)			TROPIC
	SOC (N = 104; 5 Patients Censored)	Trial (n = 64)	*P*	Cabazitaxel Arm (N = 378)
Therapy Cycles (N)			.051	
Median (IQR)	4 (3-6)	5 (3-9)		6 (3-10)
≥10 cycles (%)	14	24		28
Range	1-11	1-12		NR
Missing (%)	4	3		2
Dose Adjustment (%)			.743	
No dose reduction or delay	36	42		
Dose mitigation	33	44		
Dose reduction	15	20		NR
Dose delay	26	38		9%
Missing	31	9		
G-CSF Support (%)			.534	NR
None	80	81		
Pegfilgrastim	3	5		
Missing	17	14		
Cumulative Dose (mg)				
Median (IQR)	165 (126-300)	228 (144-422)	.026*	NR
Missing (%)	36	28		
Severe Adverse Events (%)			.967	
None	30	33		
Any	44	48		
Hospital admission	44	48		NR
Death	8	3		5
Missing	26	19		
Reason for Discontinuation (%)			.011*	
PD	72	50		48
Patient preference	2	0		2
Toxicity	4	14		18
Death	5	2		
Treatment completed	8	19		28
Other	2	2		
Missing	8	14		

Treatment outcomes are censored if patient is alive or lost to follow-up at database cutoff and time between last cabazitaxel treatment and end of follow-up is shorter than 30 days. Severe adverse events only included hospital admissions (regardless of reason of admission) and deaths (regardless of cause of death) before 30 days after last cabazitaxel infusion. Dose mitigation means either dose reduction, dose delay or both.
Abbreviations: CI = confidence interval; G-CSF = granulocyte-colony stimulating factor; IQR = interquartile range; NR = not reported; PD = progressive disease; SOC = standard of care.
*Statistically significant.

Only 42 of 173 patients had no missing data for multivariate Cox regression analysis. After imputation of missing values in all patients, in a multivariate analysis trial, participation was not prognostic for survival in the pooled data (hazard ratio = 1.00; 95% confidence interval, 0.69-1.45; $P = .999$). Longer time receiving ADT, lower PSA, and lower LDH were prognostic for longer OS, and visceral disease had a trend for shorter survival (Table 5).

Discussion

Differential Outcomes

To our knowledge, this is the first study comparing trial patients and SOC patients treated with cabazitaxel after docetaxel in a large contemporary observational studies. In this large and mature real-world cohort, patients treated with second-line cabazitaxel in a clinical trial had a mOS that was in agreement with the mOS of patients in the TROPIC trial (13.4 vs. 15.1 months).[3] The eligibility criteria of these trial patients (enrolled onto the PROSELICA, Re-Cab, CABARESC, and CABENZA trials) were similar to the TROPIC trial, with minor differences with respect to Eastern Cooperative Oncology Group performance score and estimated life expectancy (Table 6).[9,22] Although the mOS in trial patients confirms the survival outcome of the TROPIC trial, the SOC patients had a trend to shorter OS in first-line therapy after docetaxel (9.6 vs. 13.4 months).

Table 4 Treatment Outcomes

Characteristic	Cabazitaxel Second Line (N = 173)			TROPIC
	SOC (N = 109)	Trial (N = 64)	*P*	Cabazitaxel Arm (N = 378)
PSA Response				
Evaluable patients, n (%)	69 (63%)	47 (73%)		329 (87%)
PSA decline ≥ 50% (valid %)	12%	28%	.209	39%
Follow-up				
Median (IQR)	9.2 (4.2-14.9)	13.6 (6.0-22.2)		12.8 (7.8-16.9)
Events (deaths), n (%)	90 (83%)	59 (92%)		234 (62%)
Overall survival, median (95% CI)	9.6 (7.8-11.4)	13.6 (9.4-17.7)	.067	15.1 (14.1-16.3)

Abbreviations: CI = confidence interval; IQR = interquartile range; PSA = prostate-specific antigen; SOC = standard of care.

Reasons for Observed Difference Between Trial and SOC Patients

Possible reasons for the differential survival of patients in the trial and SOC subgroups include differential prognostic baseline characteristics (introduced by strict eligibility criteria of trials), cabazitaxel treatment adherence (influenced by a trial protocol), exposure to other LPDs, and the Hawthorne effect (changes in behavior or outlook associated with being under observation).[23,24]

After correction for baseline differences, time receiving ADT, PSA, and LDH were independent prognostic factors for survival, whereas treatment in a trial was not. The exclusion of patients with poorer performance status and comorbidities from clinical trials prevented the enrollment of sicker patients and subsequently limited early cancer deaths.[17] Indeed, trial patients had significantly higher hemoglobin levels, lower LDH levels, fewer visceral metastases, and fewer symptoms compared to SOC patients. At a closer

Figure 1 Overall Survival for Recipients of Second-Line Cabazitaxel Treatment (Univariate Analysis)

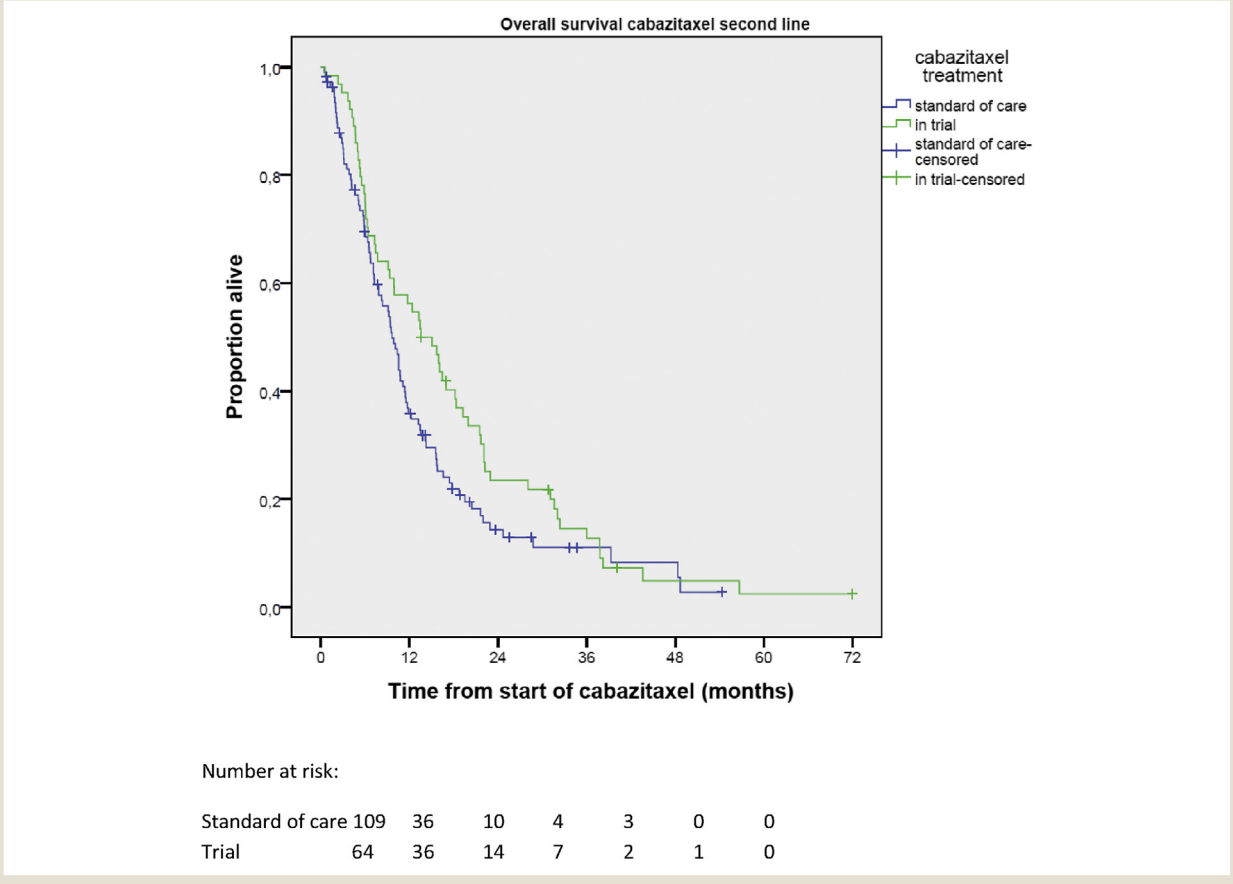

Table 5 Univariate and Multivariate Cox Proportional Hazard Analysis for Overall Survival for Cabazitaxel Second-Line Therapy

	Actual Data (N = 173, 149 Events)				Pooled Imputed Data (N = 173, 149 Events)		
	Univariate Analysis				Multivariate Analysis		
Characteristic	Events/Cases	HR	95% CI	*P*	HR	95% CI	*P*
Age	149/173	1.011	0.985-1.011	.414	1.015	0.984-1.047	.349
Charlson Comorbidity Index (%)	149/173						
7-8 vs. 6		0.974	0.681-1.392	.884			
9-10 vs. 6		0.800	0.253-2.528	.704			
> 10 vs. 6		2.540	0.350-18.407	.356			
Gleason Sum Score							
8-10 vs. ≤ 7	138/161	1.278	0.892-1.830	.181	1.102	0.720-1.687	.654
Time receiving ADT (months, continuous)	149/173	0.984	0.975-0.994	.001*	0.988	0.976-0.999	.033*
ALP (U/L, continuous)	129/146	1.000	1.000-1.001	.241	1.000	0.999-1.001	.589
PSA (μg/L, continuous)	134/155	1.000	1.000-1.000	.027*	1.000	1.000-1.000	.046*
Hemoglobin (mmol/L, continuous)	131/147	0.782	0.659-0.928	.005*	1.006	0.819-1.235	.957
LDH (U/L, continuous)	121/136	1.001	1.000-1.001	<.001*	1.001	1.000-1.001	.039*
ECOG Performance Score	118/133						
1 vs. 0		1.568	1.005-2.444	.047*	1.040	0.627-1.725	.878
>1 vs. 0		2.228	1.028-4.825	.042*	1.031	0.427-2.489	.945
Visceral Disease (%)	76/88						
Yes vs. no		3.102	1.869-5.150	<.001*	2.143	0.875-5.249	.086
Opioid Use (%)	88/98						
Yes vs. no		1.973	1.253-3.108	.003*	1.505	0.763-2.968	.215
Symptoms (%)	132/149						
Yes vs. no		1.931	1.138-3.277	.015*	1.524	0.812-2.860	.187
Time since last docetaxel (months, continuous)	143/166	0.901	0.849-0.956	.001*	0.958	0.887-1.035	.275
Docetaxel cycles (n, continuous)	146/170	0.937	0.880-0.998	.044*	0.969	0.898-1.045	.409
Trial	149/173						
Yes vs. no		0.732	0.524-1.022	.067	1.000	0.688-1.453	.999

Multivariate analysis after multiple imputation (pooled data).
Abbreviations: ADT = androgen deprivation therapy; ALP = alkaline phosphatase; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; LDH = lactate dehydrogenase; PSA = prostate-specific antigen.
*Statistically significant.

look, the cabazitaxel OS curves in first-line postdocetaxel separate directly from the start of treatment, possibly reflecting the difference in prognostic baseline parameters.

PSA response was numerically lower, but not statistically significant, for SOC patients (12%) versus trial patients (28%; $P = .209$). However, the observed PSA response appears lower than in the TROPIC and PROSELICA trials (39% and 43%, respectively). In particular, the low PSA response (12%) in the SOC subgroup may be an indicator for suboptimal selection of patients for cabazitaxel treatment. In the absence of a study protocol, timing of PSA measurement may not have been at regular intervals, leading to more missing data, as seen in the SOC patients, and therefore may have negatively influenced PSA response.

The number of docetaxel cycles has been shown to affect survival in small retrospective series, which suggests that premature discontinuation is associated with shorter OS and that maximizing docetaxel exposure may lead to increased OS. However, to our knowledge, immortal time bias was not accounted for in these studies, possibly leading to overestimation of the effect.[25-27] In a retrospective analysis of 2 clinical trials including TAX-327, no OS benefit was detected in patients receiving more than 10 cycles of docetaxel. However, receiving fewer less than 10 cycles was shown to negatively affect patients without progressive disease.[28] In a post hoc analysis of the MAINSAIL trial, an independent effect on OS by the number of docetaxel cycles administered was shown.[29] It had previously been hypothesized that administration of cabazitaxel until progression, instead of the maximum of 10 cycles in the

Table 6 Key Eligibility Criteria in Trials

Characteristic	Trial				
	TROPIC	PROSELICA	CABARESC	Re-Cab	CABENZA
Study reference[a]	NCT00417079	NCT01308580	NTR2991	NTR3233	NTR5164
Study type	Phase 3 open label randomized	Phase 3 open label randomized	Phase 2 open label randomized	Phase 1/2 open label randomized	Single-arm crossover study
Inclusion					
Life expectancy	> 2 mos	> 6 mos	Any	> 3 mos	Any
ECOG PS	0-2	0-2	0-1	0-1	0-1
Adequate organ function	Yes	Yes	Yes	Yes	Yes
Exclusion					
CNS metastases	Yes	Yes	Yes	No	Yes
Outcome, Cabazitaxel 25 mg/m^2 Arm					
Overall survival median	15.1	14.5	NA	NA	NA

Abbreviations: CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status. NA = not available.
[a]ClinicalTrials.gov NCT identifier and trialregister.nl (NTR number); results published.[3,9,22]

TROPIC trial, may have a positive effect on OS.[30] The median number of cabazitaxel cycles in the TROPIC and PROSELICA trials was 6 and 7, compared to 5 in the trial subgroup and 4 in the SOC subgroup ($P = .051$). Unfortunately, the reason of discontinuation is not well documented, and missing data may bias the results. We hypothesize that worse prognostic baseline characteristics, in particular low hemoglobin, may play a role. It remains unclear whether treatment adherence affects outcomes, including survival. This is difficult to analyze, mainly because of methodologic reasons such as immortal time bias. However, we acknowledge the possibility that the low number of cycles may have negatively influenced survival outcomes.

Although infrequent, patients in the SOC subgroup were numerically more often treated with LPD before docetaxel, leading to potential poorer outcomes because of cabazitaxel treatment in a later line in the course of mCRPC. However, the median number of

Table 7 Overview of Published Observational Studies on Second-Line Cabazitaxel Treatment

Study	Year	Population (N) and Sequence (If Reported)	Type of Study, Period	Median No. of Cycles of Cabazitaxel	Median Overall Survival (Months) and Therapy
Wissing[14]	2015	63 DCA	Multicenter retrospective, 2009-2012	7	19.1 DCA
Sonpavde[11]	2015	54 DC, 77 DCA	Multicenter retrospective, 2011-2012	5/6	7.0 DC/18.2 DCA
Moriceau[12]	2016	24 DC, 17 DAC	Single center retrospective, 2011-2014	5	11.9 DC/12.5 DAC
Hofheinz[30]	2016	527	Multicenter prospective QoL study, 2011-2014	6	16.8
Cicero[35]	2017	30	Single center retrospective, 2013-2016	8	14.8
Zschäbitz[36]	2017	18 DC, 5 XXC	Two-center retrospective, 2011-2016	5	10.0 (all patients, n = 69; no difference between groups based on line of C treatment)
Suner[13]	2016	103	Multicenter retrospective, 2012-2014	5	10.6
Carles[37]	2018	160 DC, 23 XXC	Multicenter prospective QoL study, 2012-2016	6	13.2 (all patients n = 189)
Delanoy[15]	2018	158 DCX	Multicenter retrospective, 2012-2016	7	21.0 DCX
Angelergues[16]	2018	267 DC, 124 DCX	Multicenter retrospective, 2012-2016	6/7	12.7 DC/22.7 DCX
CAPRI (this report)	2019	55 DC, 118 DCX	Multicenter retrospective, 2010-2018	3/5	4.6 DC/15.1 DCX

Abbreviations: A = abiraterone; C = cabazitaxel; D = docetaxel; QoL = quality of life; X = any treatment.

3 LPD treatments in both groups and the total duration of LPD treatment in days did not differ.

What Is Known Already

Data on real-world cabazitaxel use are increasingly reported. In several expanded-access and compassionate-use programs, inclusion and exclusion criteria still apply, and therefore, reports on these programs still have limited external validity on real-world patients.[31-34] Published reports on real-world cabazitaxel outcomes are summarized in Table 7. In retrospective studies, differential mOS is observed with regard to the registration trials (10.0-12.1 vs. 13.4-15.1 months, respectively).[3,10,38] Direct comparisons between trial patients and real-world patients are lacking, and to our knowledge, our analysis is the first to compare trial and SOC patients treated with cabazitaxel.

In retrospective studies, the range of mOS is broad (7.0-22.7 months), and patients treated with 3 LPD lines (docetaxel, cabazitaxel, and an extra line) have better mOS than patients treated with 2 LPD lines (docetaxel and cabazitaxel). In our study, patients treated with LPD after cabazitaxel had a mOS from the first cabazitaxel treatment of 15.1 months, versus 4.6 months for patients who only received best supportive care after cabazitaxel treatment. In reporting both trial and real-world outcomes, it is important to report the sequence and line of treatment as well as previous and subsequent treatments.

Limitations

Because of the retrospective nature of our registry database, the sample size was not based on power calculations but on patients available who matched the study population criteria. Furthermore, our results are limited by missing data because of the retrospective nature of our study. For multivariable analysis, we could overcome this limitation by multiple imputation methods. The comparison of SOC and trial patients is limited by the nonrandomized subgroups, reflecting trial availability and the choices of patients and physicians in real-world practice. Our results are therefore hypothesis generating.

Conclusion

We emphasize the important differences between patients treated in clinical trials and those treated in real-life practice. Patients treated with cabazitaxel in clinical trials were fitter and showed outcomes comparable to registration trials. Conversely, those treated in daily practice showed features of more aggressive disease and worse outcome. This underlines the importance of an adequate estimation of the trial eligibility and health status of mCRPC patients in daily practice to ensure optimal outcomes.

Clinical Practice Points

- Cabazitaxel has been shown to improve OS in mCRPC patients after docetaxel in the TROPIC trial. However, trial populations may not reflect a real-world population.
- From 3616 patients in the Dutch observational CAPRI registry, we identified 173 patients receiving second-line therapy.
- Trial patients had favorable prognostic factors: fewer symptoms, less visceral disease, lower LDH, higher hemoglobin, more docetaxel cycles, and longer treatment-free interval since docetaxel therapy.
- mOS was 13.6 and 9.6 months for the trial and SOC subgroups, respectively. After correction for prognostic factors, there was no difference in survival.
- Patients treated with cabazitaxel in trials were fitter and showed outcomes comparable to registration trials. Conversely, those treated in daily practice showed features of more aggressive disease and worse outcome.
- These findings emphasize the importance of an adequate estimation of the trial eligibility and health status of mCRPC patients in daily practice to ensure optimal outcomes.

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