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ARTICLE

Clinical Research

The effects of new life-prolonging drugs for metastatic castration-resistant prostate cancer (mCRPC) patients in a real-world population

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Abstract

Background In 2004 docetaxel was the first life-prolonging drug (LPD) registered for metastatic castration-resistant prostate cancer (mCRPC) patients. Between 2011 and 2014 new LPDs for mCRPC (cabazitaxel, abiraterone, enzalutamide, and radium-223) were introduced in the Netherlands. The objective of this study is to assess the impact of the introduction of new LPDs on treatment patterns and overall survival (OS) over time.

Patients and methods CRPC patients diagnosed in the years 2010–2016 in the observational, retrospective CAPRI registry (20 hospitals) were included and followed up to 2018. Two subgroups were analyzed: treatment-naïve patients (subgroup 1, $n = 3600$) and post-docetaxel patients (subgroup 2, $n = 1355$).

Results In both subgroups, the use of any LPD increased: from 57% (2010–2011) to 69% (2014–2015) in subgroup 1 and from 65% (2011–2012) to 79% (2015–2016) in subgroup 2. Chemotherapy as first mCRPC-treatment (i.e., docetaxel) and first post-docetaxel treatment (i.e., cabazitaxel or docetaxel rechallenge) decreased (46–29% and 20–9% in subgroup 1 and 2, respectively), while the use of androgen-receptor targeting treatments (ART) increased from 11% to 39% and 46% to 64% in subgroup 1 and 2, respectively. In subgroup 1, median OS (mOS) from diagnosis CRPC increased from 28.5 months to 31.0 months ($p = 0.196$). In subgroup 2, mOS from progression on docetaxel increased from 7.9 months to 12.5 months ($p < 0.001$). After multiple imputations of missing values, in multivariable cox-regression analysis with known prognostic parameters, the treatment period was independent significant for OS in subgroup 1 (2014–2015 vs. 2010–2011 with HR 0.749, $p < 0.001$) and subgroup 2 (2015–2016 vs. 2011–2012 with HR 0.811, $p = 0.037$).

Conclusion Since 2010, a larger proportion of mCRPC patients was treated with LPDs, which was related to an increased mOS.

Introduction

Prolonging overall survival (OS) is an important objective of cancer treatment. Data from cancer registries show that the 5-year survival of all types of cancer increased from 50% in 1991–1996 to 65% in 2011–2016 in the Netherlands [1]. In Europe, the largest increases in cancer survival included prostate cancer survival (age-standardized 5-year relative survival increased from 73% to 82% from 1999–2001 to 2005–2007) [2, 3]. Five-year survival is different per stage group in prostate cancer, ranging from 100% for stage I to 51% for stage IV (TNM seventh edition) in the period 2010–2015 in the Netherlands [4]. Cancer survival may be increased by improved early detection and/or more effective therapy; however, several forms of bias may influence survival results, including lengthy-time and lead-time bias [1–3].

Prostate cancer that progresses despite androgen deprivation therapy, either metastatic (m) or non-metastatic (nm), is defined as castration-resistant prostate cancer (CRPC). In 2004 docetaxel was the first available LPD for mCRPC, with a significant increase of median OS (mOS) [5].

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Between 2011 and 2014 new LPD for mCRPC (cabazitaxel [6], abiraterone [7, 8], enzalutamide [9, 10], and radium-223 [11]) were introduced in the Netherlands. Sipuleucel-T was not available in these years in the Netherlands. The reimbursement of new oncolytic follows published positive treatment outcomes, regulatory drug approval, and market authorization. In the Netherlands, the use of these oncolytic is generally conditional on positive guidance by the Dutch society of medical oncology (NVMO) committee "beoordeling van oncologische middelen (appraisal of oncolytic)" (CieBOM). The publication dates of the positive guidance by the European medicines agency and CieBOM on the aforementioned LPD are shown in Table 1.

Registration is based on the results of trials. Trial populations are subject to selection, typically enrolling younger patients with less comorbidity and features of less aggressive disease compared to real-world populations [12, 13]. These differential characteristics may lead to differential outcomes, raising the question what the effect is of these LPDs on OS in mCRPC. Furthermore, real-world data on treatment pattern changes are scarce and limited to the first treatment after mCRPC diagnosis [14, 15]. The impact of treatment pattern changes and outcomes are pivotal in the assessment of both clinical and economical effectiveness and efficacy.

The objective is to assess the impact of the introduction of new LPD treatments on treatment patterns and OS over time in a real-world population.

Methods

The study design, setting, participants, follow up and data collection of the CAPRI registry have been described in more detail [12]. In short: CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multi-center cohort study in 20 hospitals in the Netherlands. Data collection started after approval by the local medical ethics committee and hospital board. Data has been regularly updated for all patients from 2013 to 2018. The study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

Table 1 Dates of positive CieBOM guidance per LPD.

	LPD	EMA approval date	Publication date positive CieBOM-guidance[a]
Chemotherapy-naive	Docetaxel	2005	2005
	Radium-223	Sep 2013	Feb 2014
	Enzalutamide	Oct 2014	Nov 2014
	Abirateron	Nov 2012	Nov 2015[b]
Post-docetaxel	Cabazitaxel	Jan 2011	Jul 2011
	Abirateron	Jul 2011	Mar 2012
	Enzalutamide	Apr 2013	Dec 2013
	Radium-223	Sep 2013	Feb 2014

CieBOM committee "beoordeling van oncologische middelen (appraisal of oncolytics)", *LPD* life-prolonging drugs, *EMA* European medicines agency.

[a]Guidances are published in Dutch on https://www.nvmo.org/bom-type/bom/?order=disease.

[b]Negative guidance in September 2013, revised to positive guidance in November 2015.

Participants

Eligible patients had to be diagnosed with prostate cancer (defined as histologic confirmation of prostate cancer or as concluded by the treating doctor based on elevated PSA and metastatic pattern) and had disease progression despite ADT. Disease progression was defined as in the EAU CRPC definition [16] or as progression according to the treating doctor. Anti-androgen therapy following progression on ADT was considered first-line systemic therapy for CRPC. CRPC patients were retrospectively included from 2010 to 2016. Patients treated with docetaxel in the hormone-sensitive phase were excluded from this analysis. The population is an estimated 20% sample of all CRPC patients in the Netherlands.

To assess temporal real-world LPD treatment patterns, we analyzed the first LPD treatment in both treatment-naïve CRPC patients (subgroup 1) and in post-docetaxel patients (subgroup 2).

Subgroup 1 included all patients diagnosed in 2010–2016, which were divided into groups based on the date of CRPC diagnosis (2010–2011, 2012–2013, and 2014–2015). Subgroup 2 included patients treated with docetaxel for mCRPC prior to July 2016 with progression during or after docetaxel after 31 December 2010 and before 1 January 2017. Year groups were created on the docetaxel-progression date (2011–2012, 2013–2014, and 2015–2016).

Statistics

The sample size was not based on power calculations. All patients diagnosed with CRPC in the participating hospitals were included in CAPRI. Descriptive statistics were used. Differences in subgroups were tested for significance by either the Chi-square test or Kruskal–Wallis test. OS from CRPC diagnosis and progression on docetaxel to database cut-off was analyzed by Kaplan–Meier methods and Cox regression analyses. Differences were considered of statistical significance at a p-value of 0.05 or less. For imputation of missing baseline characteristics, multiple imputations by the Monte Carlo Markov Chain method were applied: the distribution of the observed data was used to estimate a set of plausible values for the missing data. The outcome variables OS time and end of follow-up state were included

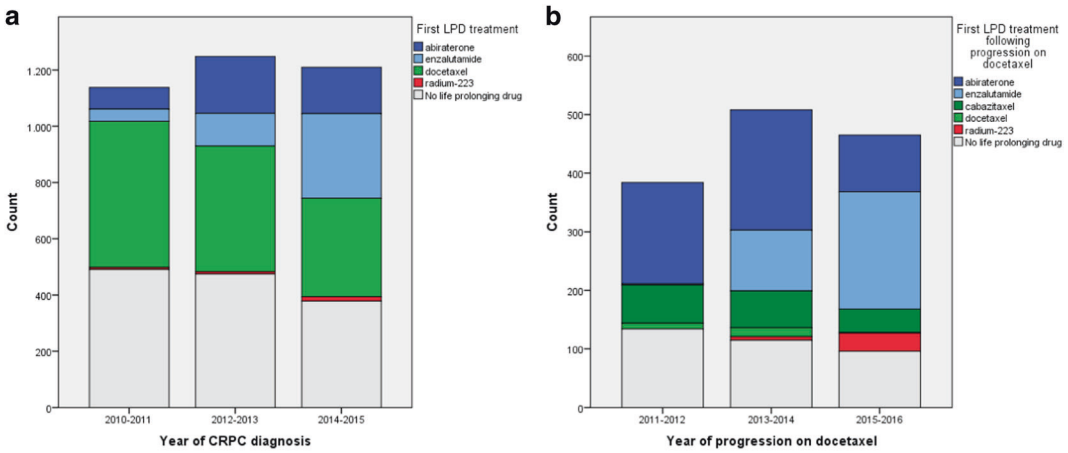

Fig. 1 Treatment patterns. a First LPD treatment after CRPC-diagnosis (subgroup 1). **b** First LPD treatment after progression on docetaxel (subgroup 2). LPD life-prolonging drug, CRPC castration resistant prostate cancer.

and used as indicators. Constraints for all imputed variables were defined based on the minimum and maximum values in the observed distribution. The variables period ADT to CRPC, PSA, ALP, and LDH were not normally distributed and transformed to approximate normality before imputation (either by taking the natural logarithm (period ADT to CRPC, PSA, ALP) or reciprocal transformation (LDH)) and after the imputation, we transformed the imputed values back to the original scale. Using the automatic imputation function, random components were incorporated into these estimated values to reflect their uncertainty. Five data sets were created and the estimates were combined in the pooled data to obtain the overall estimates and confidence intervals [17]. IBM SPSS Statistics version 22 was used for all statistical analyses.

Results

From a total of 3616 CRPC patients in the registry, 16 patients treated with docetaxel for the hormone-sensitive disease were excluded, resulting in 3600 patients (subgroup 1). Median follow-up from CRPC-diagnosis was 25.1 months. At the end of follow-up, 415 (12%) patients were alive with a median follow-up of 41.0 months (range: 24.1–95.3 months), 2432 (68%) patients died and 753 (21%) were lost to follow up.

In total, 1433 patients were treated with docetaxel before 1-7-2016. After exclusion of patients with progression in 2010 ($n = 29$) or progression after 1-1-2017 ($n = 49$), 1355 patients were analyzed in subgroup 2.

Treatment patterns

In subgroup 1 (i.e., treatment-naïve patients) any LPD treatment increased from 57% (2010–2011) to 69% (2014–2015), see Supplementary Table S1a and Fig. 1a. The use of docetaxel as the first LPD decreased from 46% (2010–2011) to 29% (2014–2015), while androgen-receptor targeting drugs (ART) increased from 11% (2010–2011) to 39% (2014–2015).

In subgroup 2 (i.e., post-docetaxel patients) LPD treatment increased from 65% (2011–2012) to 79% (2015–2016). Chemotherapy as first post-docetaxel treatment (either cabazitaxel or docetaxel rechallenge) decreased from 20% (2011–2012) to 9% (2015–2016); ART increased from 46% (2011–2012) to 64% (2015–2016) (Supplementary Table S1b and Fig. 1b).

Baseline characteristics

In subgroup 1 during the CRPC-diagnosis years, CRPC patients showed a significant and gradual increase in age, Gleason sum score and ECOG performance score (ECOG PS), a significant increase in patients with the visceral disease, and a significant and gradual decrease in time from castration to CRPC diagnosis and LDH, but not PSA and ALP (Table 2a).

In subgroup 2, patients showed a significant and gradual increase in median age, time from castration to progression on docetaxel, time from last docetaxel to progression, number of docetaxel cycles, hemoglobin, and patients with clinical progression during treatment periods (Table 2b). A gradual and significant decrease was shown in ALP, LDH, and PSA. Missing data were especially frequent (sometimes > 50%) in ECOG PS, LDH, and visceral disease in both subgroups.

Overall survival

For all patients ($n = 3600$) the mOS was 29.6 months. In subgroup 1, the median OS was 28.5, 28.5, and 31.0 months

Table 2 Baseline characteristics at (a) CRPC-diagnosis (subgroup 1) and (b) progression date of docetaxel (subgroup 2).

(a) CRPC-diagnosis (subgroup 1)

	Year of CRPC diagnosis			
Number of patients	2010–2011 1140	2012–2013 1249	2014–2015 1211	*p* value
Age (years)				<0.001
Median (IQR)	74 (68–81)	75 (68–81)	76 (70–82)	
>75 (%)	49	51	56	
Charlson comorbidity index (%)				0.794
6	60	61	63	
7–8	33	32	30	
9–10	5	5	5	
>10	2	2	2	
Missing	0	0	<1	
Gleason sum score (%)				<0.001
<8	39	33	31	
8–10	47	51	55	
Missing	15	16	14	
Time from castration to CRPC (months)				0.011
Median (IQR)	15.9 (8.9–30.8)	15.2 (8.4–30.1)	14.2 (7.9–27.6)	
Missing (%)	1	<1	0	
ECOG performance score (%)				<0.001
0	24	20	11	
1	22	17	13	
2	3	4	4	
>2	1	1	1	
Missing	50	58	70	
ALP (U/L)				0.878
Median (IQR)	105 (77–187)	105 (79–193)	108 (78–198)	
Missing (%)	40	41	31	
Hemoglobin (mmol/L)				0.247
Median (IQR)	8.1 (7.4–7.3)	8.0 (7.3–8.6)	8.0 (7.3–8.6)	
Missing (%)	36	36	31	
PSA (μg/L)				0.137
Median (IQR)	18 (6–67)	15 (6–55)	17 (5–63)	
Missing (%)	4	3	2	
Visceral disease (%)				0.047
Yes	4	3	4	
No	18	16	12	
Missing (%)	78	81	85	
Pain and/or opioid use				0.089
Yes	25	23	21	
No	42	33	16	
Missing (%)	33	44	63	
LDH (U/L)				
Median (IQR)	226 (188–329)	230 (191–313)	217 (186–268)	0.001
Missing (%)	63	61	52	

(b) Progression date of docetaxel (subgroup 2)

	Year of progression on docetaxel			
Number of patients	2011–2012 384	2013–2014 508	2015–2016 463	*p*-value
Age at progression on docetaxel (years)				0.005
Median (IQR)	71 (65–76)	72 (66–77)	72 (68–78)	
>75 (%)	30%	37%	38%	
Charlson comorbidity index at start docetaxel (%)				0.197
6	66	70	66	
7–8	30	26	29	
9–10	4	4	3	
>10	<1	<1	2	
Missing	0	0	0	
Gleason sum score (%)				0.514
<8	35	34	32	
8–10	54	56	59	
Missing	12	11	10	
Time from castration to progression on docetaxel (months)				<0.001
Median (IQR)	24 (16–34)	28 (18–44)	30 (20–50)	
Missing (%)	1	<1	0	
Time from last docetaxel to progression on docetaxel (months)				<0.001
Median (IQR)	1.5 (0.6–3.7)	2.0 (0.7–4.3)	2.3 (0.7–5.1)	
≤0 months (%)	11	9	4	
≤6 months (%)	91	86	81	
Missing (%)	4	3	1	
Docetaxel cycles				
Median (IQR)	6 (4–9)	7 (5–10)	7 (5–10)	0.001
≥10 (%)	21	27	25	
Missing (%)	1	1	0	
ECOG performance score (%)				0.310
0	10	12	10	
1	31	26	25	
2	12	13	8	
>2	5	4	2	
Missing	43	46	56	
ALP (U/L)				<0.001
Median (IQR)	161 (89–311)	144 (86–311)	120 (76–225)	
Missing (%)	34	30	19	
Hemoglobin (mmol/L)				0.039
Median (IQR)	7.1 (6.4–7.9)	7.2 (6.6–8.0)	7.5 (6.6–8.1)	
Missing (%)	30	35	41	
PSA (μg/L)				<0.001
Median (IQR)	128 (37–391)	108 (33–296)	73 (24–225)	
Missing (%)	18	19	13	
LDH (U/L)				0.001
Median (IQR)	304 (228–493)	276 (217–435)	255 (209–334)	
Missing (%)	43	50	51	
Visceral disease (%)				0.165
Yes	13	19	17	
No	34	33	37	
Missing (%)	53	47	47	
Clinical progression (%)				0.013
Yes	60	62	60	
No	21	22	32	
Missing (%)	19	16	8	

CRPC castration-resistant prostate cancer, *IQR* interquartile range, *ECOG* eastern cooperative oncology group, *ALP* alkaline phosphatase, *PSA* prostate-specific antigen, *LDH* lactate dehydrogenase.

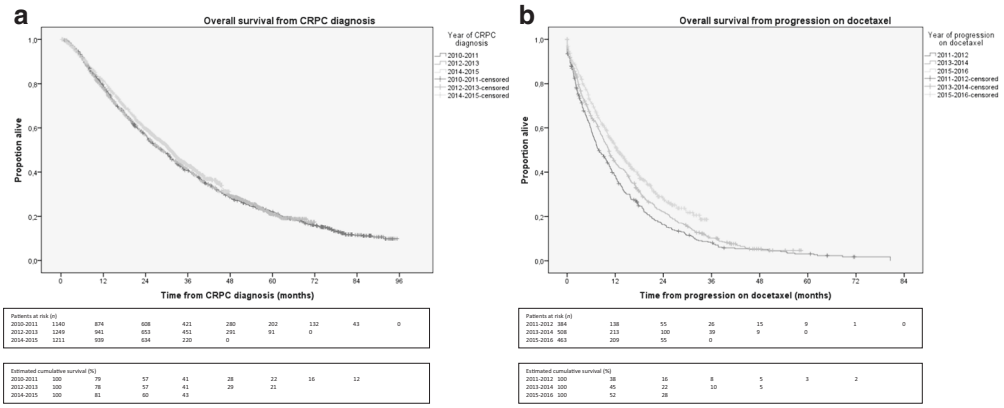

Fig. 2 Overall survival. a Overall survival from CRPC diagnosis (subgroup 1). **b** Overall survival from progression on docetaxel (subgroup 2). CRPC castration resistant prostate cancer.

for the CRPC-diagnosis 2010–2011, 2012–2013, and 2014–2015, respectively ($p = 0.196$). Twelve-months and 24-months survival increased from 79% to 81% and 57% to 60%, respectively (see Fig. 2a). OS in patients treated with LPD was 32.7 months vs. 20.8 months for patients not treated with LPD ($p < 0.0001$). Univariate prognostic factors for survival were age, Charlson comorbidity score, Gleason sum score, time from ADT tot CRPC, ALP, PSA, hemoglobin, LDH, ECOG PS, visceral disease, and pain and/or opioid use (see Table 3a). Because only 223 patients had complete data, multiple imputations of missing baseline values were performed to allow for multivariate analysis with prognostic factors. After multiple imputations, in multivariable analysis, the treatment period was significant for survival (HR 0.749 (95% CI 0.670–0.838) in 2014–2015 vs. 2010–2011, $p < 0.001$). Also, age, time from ADT tot CRPC, ALP, PSA, hemoglobin, LDH, ECOG PS, visceral disease, and pain and/or opioid use remained independent prognostic factors (see Table 3a).

In subgroup 2, mOS from progression on docetaxel increased significantly from 7.9 months to 12.5 months ($p < 0.001$); 12-months and 24-months survival increased from 38% to 52% and 16% to 28%, respectively (see Fig. 2b). OS in patients treated with LPD was 14.0 months vs. 2.0 months for patients not treated with LPD ($p < 0.0001$). Univariate prognostic factors for survival were age, Charlson comorbidity score, time since start castration, PSA, ALP, Hb, LDH, ECOG PS, visceral disease, clinical progression, time since last docetaxel and number of docetaxel cycles, and also the treatment period (see Table 3b). Only 229 patients had complete data. After multiple imputations, in multivariable analysis, the treatment period remained significant for increased survival (HR 0.811 (95% CI 0.677–0.987) in the last period vs. the first period, $p = 0.037$; see Table 3b). Time since start castration, ALP, Hb, ECOG PS, visceral disease, clinical progression, time since last docetaxel, and the number of docetaxel cycles were all associated with increased survival.

Discussion

In this large contemporary outcomes registry of CRPC patients in the Netherlands, we observed an increased survival in multivariate analyses of newly diagnosed CRPC patients and post-docetaxel patients during the years 2010–2018. In these years, several new LPD have been approved for CRPC, both treatment-naïve, and post-docetaxel. To our knowledge, this is one of the largest cohorts with long follow-up allowing for evaluation of uptake of new treatments and the effect on treatment outcomes. Results, therefore, reflect contemporary daily practice.

With the registration of new drugs, more patients were treated with at least one LPD. The observed pattern indicates the potential substitution effect of newly registered LPD, for example, abiraterone for docetaxel. After the registration of enzalutamide, no further decrease in chemotherapy use was seen. However, the frequency of abiraterone use decreased after registration of enzalutamide, especially in the post-docetaxel setting. Because both abiraterone and enzalutamide are oral drugs with similarities in mode of action, potential treatment benefit, and toxicity profile, enzalutamide can be seen as a substitute treatment option for abiraterone. The observed decrease in abiraterone use was probably driven by the registration of enzalutamide, but we expect that the future balance between abiraterone and enzalutamide will reflect patient and physician preferences also in treatment-naïve cohorts.

In treatment-naïve patients, we observed a trend towards older patients, higher Gleason sum score, and shorter time to CRPC, regardless of the treatment given. The exact

Table 3 Cox-regression analysis of OS from (a) CRPC-diagnosis (subgroup 1) and (b) progression on docetaxel (subgroup 2).

(a) CRPC-diagnosis (subgroup 1)

	Univariable analysis of actual data				Multivariable analysis of pooled imputed data		
	Events/cases	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	2432/3600	1.018	1.013–1.022	<0.001	1.021	1.015–1.026	<0.001
Charlson comorbidity index	2431/3598						
7–8 vs. 6		1.196	1.097–1.303	<0.001	1.096	0.987–1.217	0.086
9–10 vs. 6		1.315	1.104–1.566	0.002	1.238	0.957–1.602	0.099
>10 vs. 6		2.605	1.953–3.475	<0.001	2.173	1.564–3.020	<0.001
Gleason sum score	2055/3078						
8–10 vs. ≤7		1.145	1.048–1.251	0.003	1.041	0.927–1.169	0.483
Period ADT to CRPC (months, cont.)	2426/3588	0.986	0.984–0.988	<0.001	0.987	0.985–0.989	<0.001
ALP (U/L, cont.)	1617/2254	1.001	1.001–1.001	<0.001	1.001	1.001–1.001	<0.001
PSA (μg/L, cont.)	2359/3491	1.000	1.000–1.000	<0.001	1.000	1.000–1.000	<0.001
Hemoglobin (mmol/L, cont.)	1701/2361	0.608	0.579–0.638	<0.001	0.731	0.698–0.766	<0.001
LDH (U/L, cont.) LOG (LDH)	1091/1481	1.001	1.001–1.001	<0.001 <0.001	1.000	1.000–1.001	0.016
ECOG performance score	1066/1452						
1 vs. 0		1.794	1.574–2.044	<0.001	1.336	1.175–1.520	<0.001
>1 vs. 0		4.686	3.876–5.665	<0.001	2.844	2.191–3.692	<0.001
Visceral disease	500/672						
Yes vs. No		1.563	1.257–1.943	<0.001	1.224	1.004–1.494	0.047
Pain and/or opioid use							
Yes vs. No	1432/1916	2.013	1.811–2.239	<0.001	1.375	1.188–1.592	<0.001
Year of CRPC diagnosis	2432/3600						
2012–2013 vs. 2010–2011		0.994	0.905–1.092	0.899	0.893	0.810–0.983	0.022
2014–2015 vs. 2010–2011		0.915	0.823–1.106	0.098	0.749	0.670–0.838	<0.001

(b) Progression on docetaxel (subgroup 2)

	Univariable analysis of actual data				Multivariable analysis of pooled imputed data ($n = 1355$)		
	Events/cases	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1096/1355	1.009	1.001–1.017	0.037	1.002	0.993–1.012	0.622
Charlson comorbidity index	1096/1355						
7–8 vs. 6		1.071	0.938–1.222	0.311	1.028	0.897–1.179	0.690
9–10 vs. 6		1.362	1.019–1.819	0.037	1.068	0.762–1.499	0.699
>10 vs. 6		1.834	0.913–3.685	0.088	1.856	0.802–4.294	0.146
Gleason sum score							
8–10 vs. ≤7	981/1211	1.075	0.945–1.224	0.272	0.895	0.772–1.038	0.140
Period on ADT (months, cont.)	1091/1350	0.988	0.985–0.991	<0.001	0.992	0.989–0.995	<0.001
ALP (U/L, cont.)	795/983	1.001	1.001–1.002	<0.001	1.001	1.000–1.001	<0.001
PSA (μg/L, cont.)	904/1131	1.000	1.000–1.000	<0.001	1.000	1.000–1.000	0.055
Hemoglobin (mmol/L, cont.)	726/875	0.618	0.574–0.666	<0.001	0.748	0.695–0.804	<0.001
LDH (U/L, cont.)	584/702	1.000	1.000–1.001	<0.001	1.000	1.000–1.000	0.067
ECOG performance score	582/698						
1 vs. 0		1.454	1.160–1.822	0.001	1.113	0.903–1.373	0.307
>1 vs. 0		3.619	2.826–4.635	<0.001	1.517	1.074–2.145	0.022
Visceral disease	552/695						
Yes vs. no		1.650	1.383–1.970	<0.001	1.478	1.235–1.768	<0.001
Clinical progression	942/1167						
Yes vs. no		1.807	1.562–2.091	<0.001	1.245	1.036–1.497	0.021
Time since last docetaxel and progression (months, cont.)	1070/1321	0.926	0.909–0.944	<0.001	0.971	0.952–0.991	0.005
Docetaxel cycles (*n*, cont.)	1089/1346	0.899	0.880–0.919	<0.001	0.951	0.929–0.974	<0.001
Year of progression on docetaxel	1096/1355						
2011–2012		ref					
2013–2014		0.849	0.738–0.978	0.023	0.887	0.749–1.050	0.160
2015–2016		0.686	0.587–0.802	<0.001	0.811	0.667–0.987	0.037

OS overall survival, *CRPC* castration-resistant prostate cancer, *HR* hazard ratio, *CI* confidence interval, *ADT* androgen deprivation therapy, *ALP* alkaline phosphatase, *PSA* prostate-specific antigen, *LDH* lactate dehydrogenase, *ECOG* eastern cooperative oncology group.

reason for the shift in these characteristics is unclear. We speculate that this is driven mainly by the differential diagnostic and therapeutic behavior of clinicians. Differential referral patterns from urologists to medical oncologists are not the reason, because we included all patients from both departments in all participating hospitals. One could speculate that the indication for first-line ADT for hormone-sensitive metastatic disease moved towards this profile, or that more patients in this profile were referred to a participating CAPRI hospital. Moreover, clinicians may have monitored patients more strictly because of the availability of more treatment options leading to a shorter time to CRPC. Interestingly, the same shift in age and Gleason sum score was seen in a recent single-center analysis [18]. The shift in characteristics may have influenced the observed switch from chemotherapy to ART.

Similar to the treatment-naïve cohort, the baseline profile of post-docetaxel patients showed a trend to higher age with less aggressive characteristics (i.e., longer time from castration to progression on docetaxel, longer time from last docetaxel to progression, the higher number of docetaxel cycles, higher hemoglobin and lower ALP, LDH, and PSA). We hypothesize that increasing clinician experience or the availability of post-docetaxel drugs may have decreased the threshold for referral to the medical oncologist and subsequent docetaxel treatment. Moreover, patients with aggressive disease are likely to start docetaxel early and progress early, whereas patients with the less aggressive disease are more likely to have a more protracted course and thus progress in later years. In contrast, with the increasing pre-docetaxel treatment options the prognostic characteristics at progression on docetaxel may be expected to shift towards more aggressive disease characteristics and a decline of patient condition. However, this was not observed in our population.

Our analysis showed that OS increased over time. Prognostic models have been developed for both treatment-naïve and post-docetaxel CRPC-patients, including ECOG PS, ALP, PSA, hemoglobin, and visceral disease. The treatment-naïve prognostic model also included LDH and Gleason sum score, while the post-docetaxel model included time since docetaxel use, pain, and time since castration [19, 20]. We studied the same characteristics in our population with similar results: we confirmed all known prognostic factors in both univariable and multivariable analyses, in both subgroups (except for measurable disease, which was not registered in our database). Since both subgroups tended to have better prognostic profiles in later treatment periods, this can partially explain the increase in OS. However, treatment periods remained prognostic after correction for known prognostic factors. The median OS in the last period (2014–2015) of the treatment-naïve patients compares favorably to previous reports. Previously reported mOS from mCRPC diagnosis in observational studies in different periods ranges from 9–15 months (before 2004) [21–23], 11–26 months (2004–2010) [18, 24, 25] to 33–34 months (from 2010) [18, 25], although these studies differ in methods and should be compared with caution.

Limitations include the clinical scope that is limited by the current use of some LPD in the hormone-sensitive phase. The high number of missing values, inherent to the retrospective design of this study leads to statistical challenges. Missing values on baseline characteristics reflect the incomplete evaluation of patients or lack of structured reporting in daily practice. This was particularly shown for ECOG PS, LDH, and visceral status for subgroup 1, and to a lesser extent in subgroup 2. This warrants better documentation, especially at CRPC-diagnosis. To discard all patients with incomplete data would result in a small population and a substantial loss in precision and power. Moreover, due to the baseline and survival differences between patients with complete data and incomplete data (see supplementary Table S2), this would lead to invalid (non-representative) outcomes. Imputation of missing baseline data did provide a valid solution for multivariable analyses and allowed to use all patients. We were also not able to analyze the reasons for the treatment decisions made. Treatment patterns could have shifted due to the preferences and experience of physicians. However, we did not have insight into these aspects, since they are not structurally captured in medical records.

Conclusion

The introduction of new LPD in the Netherlands resulted in a marked increase in patients treated, a shift in the characteristics of the population treated, and a significant and relevant decrease in the hazard for death.

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Compliance with ethical standards

Conflict of interest HMW reports travel expenses paid by Ipsen and honoraria from Roche and Astellas. MCPK reports travel expenses from Ipsen. AJMvdE reports study grants from Sanofi and Roche, travel expenses from MSD Oncology, Roche, Pfizer, and Sanofi, honoraria from Bristol-Myers Squibb, and consulting/advisory role for Bristol-Myers Squibb, MSD Oncology, Amgen, Roche, Novartis, Sanofi, Pfizer, Ipsen, and Merck. RdW reports consulting/advisory role for Sanofi, Merck Sharp&Dohme, Roche/Genentech, Janssen, Bayer, Clivis; honoraria from Sanofi, Merck Sharp&Dohme; and research funding from Sanofi and Bayer. AMB reports research funding from Sanofi, Astellas, and Bayer; consulting/advisory role for Sanofi,

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